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Commentary

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The comprehensive Update by Vassal published in this issue [1] is a timely reminder for the progress that has been made, and the challenges that remain, in the development of better drugs for the treatment of paediatric cancer. The treatment of malignant disease in children has shown a progressive improvement over many years, such that most children – over 70% – can expect eventual cure. This improvement has coincided with the development of systematic treatment strategies, each building on the success of its predecessor. For all such treatments – until perhaps very recently – the goals of achieving a response, then remission, and eventual cure have defined how treatment protocols develop. These goals are still appropriate for most patients, for whom conventional chemotherapy, radiotherapy and surgery are effective. For these patients, the place for chemotherapeutic drugs is quite clear.

However, a proportion of children will fail to respond, fail to remit or will relapse after conventional therapy. Some will be cured after a second or even third round of conventional treatment, but the chance of eventual cure is small, often requires more intensive therapy, and comes at the cost of significantly higher toxicity. For this group current strategies are, by definition, less satisfactory.

For those children who are incurable by conventional means, strategies may involve:

- Intensification of therapy: Stem cell growth factors, or reinfusion, from autologous or matched donors, may allow sufficient chemotherapy to be given to overcome resistance in tumour cells. In acute lymphoblastic leukaemia (ALL), bone marrow transplantation from allogeneic donors undoubtedly adds a graft versus leukaemia effect, but it is the intensification of therapy which leads to cure for most patients.
- Novel schedules of administration: The use of low-dose, "metronomic" chemotherapy, which lacks significant toxicity, has been effective in some tumours, where conventional strategies have failed. Such an effect has been postulated for chronic, low-dose administration of etoposide, and, more recently, for vinblastine in children with primary central nervous system tumours. The prolonged, continuation or "maintenance" phase of ALL therapy may have a similar mechanism of action [2].
- Novel drugs with a cytotoxic effect: This has been a main thrust over the last 20 years, and has led to the development of many conventional chemotherapy agents, including temozolomide, taxoids and irinotecan. The rate of development of such agents has fallen, and for many drugs, there has been no real clinical benefit in terms of activity. As patients receive progressively more intensive therapy, the incremental benefit of each new treatment is likely to be smaller.

The likelihood of achieving a response with any treatment is less in heavily pre-treated patients, and there is a danger that conventional methods of evaluation will fail to identify potentially useful agents. The "up-front window" type of study is one way in which a true response rate in untreated or relatively untreated patients can be assessed, but there is concern that patients treated in this way may receive sub-optimal therapy at a key point in treatment [3].

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Increasingly, the ability to identify cellular targets within the transformed cell has led to a new approach to the development of anti-tumour drugs, and it is hoped that, by identifying such targets, agents can be "fast-tracked" to reach the target patient population and routine clinical use without the delays that are seen at present. Our ability to measure inhibition of target enzymes or receptors may reduce the danger of inadequate dosing, and for many such agents, the optimal dose may be below the maximum tolerated dose. Although these agents are not "conventional" chemotherapeutic drugs, and their action may not be to cause cell death, the clinical goal remains the continuing good health of the affected patient. In this respect, optimal biological doses identified using surrogate markers may or may not represent the dose that gives the child the best chance of benefiting clinically from the drug. Examples include the use of Imatanib mesylate (Glivec) in Chronic Myeloid Leukaemia or the use of anti-angiogenic agents in a prolonged, low-dose schedule.

Chemotherapy is central to cure for most children with cancer, and for some, such as those with leukaemia, it is the only modality necessary. Most of these patients receive active agents, achieve adequate exposure in all "biological compartments", and have a tumour cell population that remains sensitive to one or more of the drugs used. Survival after leukaemia has risen in each 5-year period since the 1980's, and for these patients, chemotherapy has clearly not yet reached its limit. New, active chemotherapy agents, such as cladribine, have been and will be developed, and it is hoped that their inclusion at earlier stages of treatment will led to even greater success. The limit for conventional chemotherapy comes for those patients who, after repeated cycles of treatment and relapse, or because of adverse biological characteristics *de novo*, fail to respond or remit. For these patients, the novel approaches currently under investigation will become the conventional chemotherapy of the future.

Additional ways in which both conventional cytotoxic and targeted therapies will be optimised will include patient stratification and dose adjustment on the basis of both host pharmacogenetics and tumour molecular pathology. As is often the case, paediatric oncologists are already at the forefront of these fields. The stratification of neuroblastoma therapy on the basis of *MYCN* status, and the centralisation of treatment for childhood cancers readily facilitates approaches like these.

Overall, there is no reason to believe that chemotherapy has reached any limits for the treatment of childhood cancers; there is no shortage of new drugs or ideas to optimise existing therapies. Barriers are often logistical rather than scientific and the challenge for the paediatric oncology community is to break through these obstacles and demonstrate that the only limit to chemotherapy is 100% cure.

Conflict of interest statement

None declared.

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