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Perspectives

High Dose Chemo-radiotherapy for Sensitive Tumors: Is Sequential Better Than Concurrent Drug Delivery?

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CONVINCING evidence indicates that the most important reason for drug treatment failure in cancer is primary drug resistance. Goldie and Coldman [1], by shifting the main emphasis of cancer therapy from tumor cell kinetics to tumor cell resistance, provided an adequate explanation for the failure of early clinical attempts to achieve durable complete remissions, and their hypothesis prompted the development of new effective programs employing non-cross-resistant regimens. According to the basic assumption of the Goldie–Coldman hypothesis, tumors are curable by chemotherapy in the absence of permanently multiple resistant cell lines. The Goldie and Coldman model therefore provides the rationale for the administration of multiple drugs over single agents and supports the simultaneous delivery of all available effective drugs. In addition, the model calls for the highest possible dose of anticancer drugs to increase the fractional cell kill to the maximum possible level, and thus lead to total eradication of drug sensitive tumor cells.

In clinical practice, these two objectives are difficult, if not impossible, to reconcile. As a consequence of increased overall toxicity, the simultaneous delivery of several chemotherapeutic agents becomes feasible only at the expense of a substantial dose reduction of the drugs included in a given combination compared to the dose of the same drug(s) when used as single agent. Thus, if we consider resistance as the most important single factor for treatment failure, present combination drug schedules are expected to work only in the most sensitive tumors, i.e. when the dose–response curve for tumor cytoreduction falls within the range of doses that when administered *simultaneously* are tolerable to the host.

An alternative approach to treatment of marginally sensitive tumors may be represented by high dose chemo-radiotherapy followed by bone marrow rescue (autologous, syngeneic or allogeneic) to overcome the otherwise irreversible myelosuppression. The major limitation of these treatments is early toxicity, with a substantial number of life-threatening complications and toxic deaths, that make it virtually impossible to deliver more than one cycle of high dose chemo-radiotherapy in the single patient [2]. Thus, high dose regimens are essentially 'single shot' experiments. As such, they disregard, besides other mainstays of cancer treatment, the well established principle that most chemotherapy is directed against proliferating cells, while a significant number of clonogenic cells within an unperturbed tumor are non-proliferating. This overlooking of the cell kinetic aspect might help to explain why the dramatic clinical remissions often observed with this approach in relapsed or resistant tumors are usually short lived. Of course, one might rely on high dose chemo-radiotherapy as a late intensification (consolidation) treatment. This modality, as currently applied, has not shown to increase convincingly the cure rate in non-hematological malignancies [3–6]. A result not totally unexpected

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if we consider that the cells we plan to eradicate through the high dose consolidation phase have already been exposed to repeated courses of standard dose chemotherapy; that is to suboptimal treatment that might have favored the emergence of multiple-resistant cell lines.

In an effort to reconcile tumor cell kinetics and tumor cell resistance, we have designed a number of sequential high dose chemo-radiotherapeutic regimens that are currently being tested for toxicity and activity in malignant lymphomas and other drug-sensitive solid tumors. One prototype regimen is outlined in Table 1. As shown it supports the delivery, at the shortest possible intervals, of non-cross-resistant drugs at the highest (or nearly so) tolerable doses. The regimen has several distinctive features that are worth analyzing in detail.

PROTOTYPE REGIMEN

The starting drug is cyclophosphamide which can be safely given in doses up to 7 g/m^2 [4, 7]. Bone marrow support is not required since myelopoiesis fully recovers about 2 weeks from treatment and is not accelerated by giving marrow infusion [8]. Like most alkylating agents, cyclophosphamide shows, at least in experimental tumors, a log–linear relationship between cell kill and tumor cytotoxic drug dose [9]. This drug does not have a strong proliferation-dependent cytotoxicity and thus will also kill cells which are out of the cell cycle [10]. This regimen is expected to recruit the non-proliferating cells into a proliferative, more chemosensitive phase as best seen in fast growing tumors such as Burkitt's lymphoma and small cell lung carcinoma. In several instances of bulky tumor masses, nearly stationary in growth as suggested by a very slow rate of volume increase in tumor volume, we have observed considerable and rapid reduction of tumor volume (up to 80% within 10–14 days) followed by an exceedingly rapid regrowth. A second drug course delivered in this phase results in a very rapid tumor regression, often complete. Finally, even at these very high doses, cyclophosphamide spares the hematopoietic stem cells. In fact this alkylating agent induces a proliferative wave that, approximately 2 weeks later, results in a several-fold increase of clonogenic myelopoietic cells both in the bone marrow and in the peripheral blood [11–13]. Harvesting the bone marrow and/or circulating stem cells at this stage appears attractive for two reasons. First, the recovery time following bone marrow reinfusion is reduced to a minimum, as consequence of the very high number of collected bone marrow cells and, possibly, of the more advanced developmental stage of circulating progenitor cells requiring a shorter interval to go to maturation. All patients treated so far with a fully myeloablative regimen (total body irradiation 12.5 Gy combined with melphalan 160–180 mg/m^2) and autografted with bone marrow and circulating stem cells harvested on days 17–19 after cyclophosphamide, experienced a very prompt and complete hematological reconstitution. In fact, they showed a very low requirement for erythrocyte and platelet transfusions, recovered more than 500 leukocytes/μl within 9 days, more than 500 neutrophils within 12 days and could be discharged in less than three weeks after autografting [13]. The second attractive reason for stem cell harvesting following high dose cyclophosphamide is that the treatment is expected to eliminate or substantially reduce sensitive tumor cells contaminating the bone marrow (*in vivo* 'purging'). This has been documented by us (unpublished results) in two patients with small cell lung carcinoma, whose bone marrow contained a sizable proportion of immunoreactive tumor cells before therapy, and none 2 weeks following high dose cyclophosphamide. Because of the bone marrow stem cell sparing properties of cyclophosphamide [8, 14], patients treated with this drug are expected to enjoy a substantial benefit from the use of recombinant human colony-stimulating factor (GM-CSF)

Table 1. High dose sequential regimen. Prototype schedule

Drug or procedure	Dose (mg/m^2)	Via	Day*
Cyclophosphamide	7000	i.v.	0
Leukapheresis			14–18 (max 4)
Bone marrow harvest			19
Vincristine	1.4	i.v.	21
Methotrexate + leukovorin rescue	8000	i.v.	21
Cisplatin	60	i.v.	26, 33
Total body irradiation	12.5 Gy (tot.)		43, 44, 45
Melphalan	120–160	i.v.	46
Stem cell autografting			47

*Days are indicative, with changes allowing for clinical and hematological recovery from previous chemotherapy.

as a means to accelerate hematopoietic recovery following chemotherapy-induced myelosuppression [15–17]. In fact all five consecutive patients so far treated with 8 μg/kg/day GM-CSF following cyclophosphamide (7 g/m^2) have shown a significantly reduced duration and severity of bone marrow aplasia [18]. Interestingly, GM-CSF treatment resulted in a further increase in the number of circulating myeloid stem cells, up to 15,000 CFU-GM/μl of peripheral blood (Tarella C, in preparation). When these cells are harvested and infused in combination with bone marrow cells, all three patients treated so far experienced an exceedingly rapid hematopoietic recovery involving both granulocytes and platelets. The patient in Fig. 1, for example, following a fully myeloablative treatment, required only one prophylactic platelet transfusion, reached >500 neutrophils/μl on day 8, >1000 on day 10, >10,000 on day 12 and unsupported platelet count rose to >100,000/μl on day 13 [18]. As further improvement, one might foresee the use of these GM-CSF-exposed circulating cells as the only source of myeloid stem cells, and the infusion of GM-CSF in the post-transplant period. Nonetheless, if present results are confirmed in larger series, non-myeloid toxicity will remain the only limiting toxicity to high-dose chemoradiotherapy.

The second phase of the treatment sequence is delivered as soon as myelopoiesis recovers, usually on day 20 after cyclophosphamide. Two of the drugs (vincristine and methotrexate) are class II phase specific anticancer agents, whose activity is expected to be maximal following the initial recruiting course of cyclophosphamide. Their association does not require reduction of the doses when used as single agents and is possibly synergic [19]. Most important, compared with other phase-specific agents that can be used in high doses (e.g. cytarabine), vincristine and methotrexate are non-marrow toxic drugs and obviate the risk of a second myelosuppressive treatment during early recovery of the marrow (days 16–21). Cisplatin has potential synergism with antimetabolites [20] and, up to 120 mg/m^2, its marrow toxicity does not require major changes in the treatment schedule.

Finally, a class I cycle-non-specific agent (ionizing radiation) and a class III specific agent (melphalan) are administered with the aim to destroy residual non-proliferating tumor cells. Only this final phase requires bone marrow rescue.

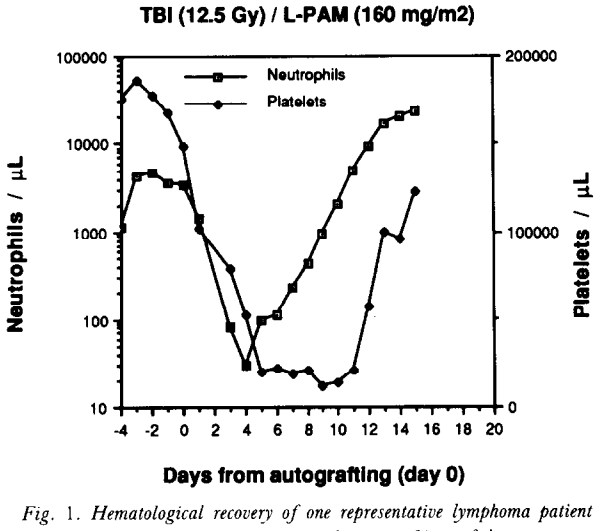

Fig. 1. Hematological recovery of one representative lymphoma patient following myeloablative treatment and autografting of bone marrow (4.7 × 10^8 nucleated cells/kg) plus GM-CSF-exposed peripheral blood stem cells (3.3 × 10^8 mononuclear cells/kg).

CLINICAL FINDINGS

The high dose sequential regimen outlined in Table 1 has been tested so far in 17 adult and four pediatric patients with advanced stage Hodgkin's disease at the time of first treatment failure after primary chemotherapy. In spite of the concern for at least additive toxicity, the three-cycle course proved to be well tolerated with an overall morbidity and mortality comparable to single-course high dose regimens requiring marrow support (two infectious deaths). This less than expected toxicity is best explained by the flexibility of the schedule. By allowing adjustments of drug doses and intervals between doses to cope with clinical variables, this protocol permits the administration of drugs safely, relative to the extremely high dose intensity achieved. In particular, due to the high efficacy of the first two treatment phases, even patients with a low starting performance status underwent the most toxic, final phase of treatment in much improved general conditions. More recently, the use of GM-CSF-exposed circulating stem cells [18] promises to virtually eliminate the infectious death toll of high dose regimens.

Making allowance for the short follow up and the limited number of patients, early results appear promising: 87.5% of refractory or relapsed adult Hodgkin's disease patients, some of whom end stages, achieved complete tumor remission. Encouraged by these results, we are now exploring the potential of high dose sequential chemo-radiotherapy (chemotherapy plus total body as well as local-regional irradiation) as a first-line therapy in advanced stage, intermediate and high-grade non-Hodgkin's lymphoma (eight patients). The prospective randomized study compares MACOP-B regimen (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin [21]) vs. high dose sequential chemo-radiotherapy. In addition, we have developed a slightly different protocol including as a final step a higher melphalan dose (200 mg/m^2) without total body irradiation. This approach is being applied to patients with

inflammatory breast cancer (12 patients) and primary resectable breast cancer with more than 10 histologically involved axillary nodes (six patients).

Finally, we would like to stress that some of the informative principles of high dose sequential chemo-radiotherapy are the same as those inspiring hematological treatments, where increasing intensity of the *first-line induction* regimens has resulted in a significantly greater proportion of patients becoming long-term survivors, in spite of increased toxicity.

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REFERENCES

1. Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979, **63**, 1727–1733.
2. Vallekoop L, Dickie KA, Zander AR *et al.* Repeated high-dose cyclophosphamide, BCNU and VP-16-213 and autologous bone marrow transplantation in adult acute lymphocytic leukemia in first remission. *Eur J Cancer Clin Oncol* 1984, **20**, 593–599.
3. Souhami RL, Finn G, Gregory WM *et al.* High-dose cyclophosphamide in small-cell carcinoma of the lung. *J Clin Oncol* 1985, **3**, 958–963.
4. Smith IE, Evans BD, Harland SJ *et al.* High-dose cyclophosphamide with autologous bone marrow rescue after conventional chemotherapy in the treatment of small cell lung carcinoma. *Cancer Chemother Pharmacol* 1985, **14**, 120–124.
5. Cunningham D, Banham SW, Hutcheon AH *et al.* High-dose cyclophosphamide and VP 16 as late dosage intensification therapy for small cell carcinoma of lung. *Cancer Chemother Pharmacol* 1985, **15**, 303–306.
6. Verdonck LF, Dekker AW, Vendrick PJ *et al.* Intensive cytoreduction therapy followed by autologous marrow transplantation for patients with hematological malignancies or solid tumors. *Cancer* 1987, **60**, 289–295.
7. Souhami RL, Harper PG, Linch D *et al.* High-dose cyclophosphamide with autologous marrow transplantation as initial treatment of small cell carcinoma of the bronchus. *Cancer Chemother Pharmacol* 1982, **8**, 31–34.
8. Smith IE, Evans BD, Millar JL. Autologous bone marrow rescue is unnecessary after very high-dose cyclophosphamide. *Lancet* 1983, **1**, 76–77.
9. Bruce WR, Meeker BE, Valeriote FA. Comparison of the sensitivity of normal hemopoietic and transplanted lymphoma colony forming cells chemotherapeutic agents administered *in vivo*. *J Natl Cancer Inst* 1966, **36**, 233–245.
10. Hill BT, Baserga R. The cell cycle and its significance for cancer treatment. *Cancer Treat Rev* 1975, **2**, 159–175.
11. Lohrmann HP, Schreml W, Fliedner TM *et al.* Reaction of human granulopoiesis to high dose cyclophosphamide therapy. *Exp Hematol* 1978, **6** (Suppl 3), 49.
12. Korbling M, Martin H, Fliedner TM. Autologous blood stem cell transplantation. In: Gale RP, Champlin RE, eds. *Proceedings of the Keystone Meeting on Bone Marrow Transplantation.* New York, Alan Liss, 1986, 1–12.
13. Gianni AM, Bregni M, Siena S *et al.* Rapid and complete hemopoietic reconstitution following combined transplantation of autologous blood and bone marrow cells. A changing role for high-dose chemo-radiotherapy? *Hematol Oncol* 1989, **7**, 139–148.
14. Bergsagel DE. An assessment of massive-dose chemotherapy of malignant disease. *Can Med Assoc J* 1971, **104**, 31–36.
15. Morstyn G, Campbell L, Souza LM *et al.* Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988, **1**, 667–672.
16. Gabrilove JL, Jakubowski A, Sher H *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988, **318**, 1414–1422.
17. Antman KS, Griffin JD, Elias A *et al.* Effect of recombinant human granulocyte colony-stimulating factor on chemotherapy-induced myelosuppression. *N Engl J Med* 1988, **319**, 593–598.
18. Gianni AM, Siena S, Bregni M *et al.* Very rapid and complete haematopoietic reconstitution following myeloablative treatments: the role of circulating stem cells harvested after high-dose cyclophosphamide and GM-CSF. In: Dicke KA, Spitzer G, Jagannath S, eds. *Autologous Bone Marrow Transplantation.* Houston, The University of Texas Press (in press), Vol. IV.
19. Zager RF, Frisby SA, Oliverio VT. The effects of antibiotics and cancer chemotherapeutic agents on cellular transport and antitumor activity of methotrexate in L-1210 murine leukemia. *Cancer Res* 1973, **33**, 1670–1676.
20. Ferrari L, Bajetta E, Gianni L *et al.* Four drug sequential regimen in advanced breast cancer. *Breast Cancer Res Treat* 1987, **10**, 151–157.
21. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann Intern Med* 1985, **102**, 596–602.