PERGAMON

European Journal of Cancer 39 (2003) 1497–1500

European Journal of Cancer

www.ejconline.com

Editorial

Chemotherapy in developing countries—is less better?

I. Magrath*

International Network for Cancer Research, Institut Pasteur, 642 rue Engeland, Brussels 1180, Belgium

Received 8 January 2003; accepted 18 March 2003

Cancer chemotherapy, as patients who receive it and those who care for them are only too well aware, can be a double-edged sword. Conventional chemotherapeutic agents are, in fact, cell poisons whose dosage and administration must be carefully controlled if susceptible cancers are to be eradicated without causing irreparable harm to patients. Medical oncologists have, therefore, spent much of the second half of the last century learning, through empirical clinical trials, the maximal tolerated doses of individual drugs or combinations of drugs, and determining their cost–benefit ratios (therapeutic indices). Almost all of this research has been done in the affluent nations, and it should not be assumed that it applies equally to developing countries where the three determinants of the success or failure of chemotherapy—the treatment itself, the tumour and the patient—may differ markedly. In addition to genetic differences in the tumour and in the host that may influence chemosensitivity and pharmacogenetics [1–3], co-morbidities such as malnutrition, tuberculosis, malaria or hepatitis may have a major impact on treatment tolerance in low-resource settings [4,5].

Treatment outcome may also be different if regimens are modified because drugs are unavailable or unaffordable, because of poor protocol adherence by the doctor or patient, or because of excessive toxicity resulting from inadequate supportive care. Almost all types of cancer in developing countries tend to be more extensive at presentation because of delays in diagnosis and limited access to diagnostic and treatment facilities. This is especially likely to be the case in rural settings, where medical resources tend to be particularly scarce [6]. Consequently, most of these patients fall into high-risk groups requiring more toxic and more expensive therapy, a problem that is compounded by the fact that poor patients rarely have insurance [7]. In effect, a vicious cycle is created whereby the limited resources themselves, by decreasing access, result not only in worse outcomes, but create an even greater need for resources, thus further limiting access and perpetuating the cycle (Fig. 1). Socio-economic deprivation also results in patients failing to complete therapy or being subsequently lost to follow-up. Thus, even the limited resources available are often inefficiently used and there is minimal evidence upon which to base standard treatment approaches or generate hypothesis-driven research. Whilst health professionals in developing countries who deal with cancer are aware that their patients tend to have very advanced disease compared with those seen in affluent countries, they are often overwhelmed by patient numbers and a lack of necessary resources and training to begin addressing the problem. All too often the situation is accepted as inevitable, and attempts to break the vicious cycle are either never started, or are rapidly abandoned.

What is to be done?

Breaking the vicious cycle

Among several possible approaches to ameliorating the vicious cycle, cancer prevention is often stressed as deserving a particularly high priority in developing countries on the grounds that it is less expensive than attempts to cure and requires fewer human and physical resources. Prevention, however, is applicable to only a fraction of tumours and even in affluent nations population-scale successes have taken decades to materialise. In any case, the same approaches cannot easily be applied to developing countries in which a high fraction of the population is poor, uneducated and illiterate and where cultural differences must be taken into consideration. It is a sobering fact that countries in which cancer prevention is most advanced (the affluent countries) have the highest incidence rates, albeit with a somewhat different pattern of cancer type. Thus, although prevention programmes should be an important

* Tel.: +32-2-373-9325; fax: +32-2-373-3282.
E-mail address: imagrath@inctr.be (I. Magrath).

0959-8049/03/$ - see front matter
doi:10.1016/S0959-8049(03)00296-X

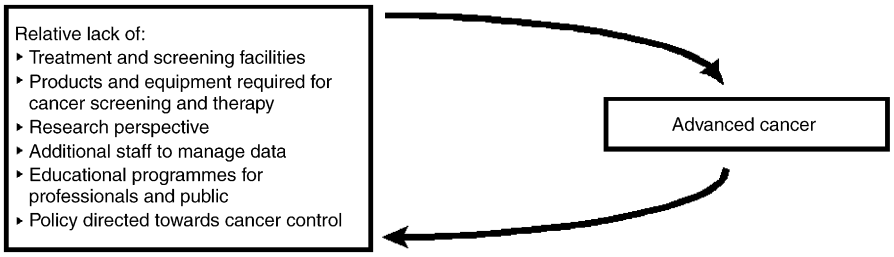

Fig. 1. The vicious cycle.

element of any cancer control programme, they cannot be the only, or even the primary approach to cancer control, except perhaps in the context of specific cancers (e.g., tobacco-related cancers). Patients who already have cancer cannot simply be ignored. The International Agency for Research on Cancer has predicted that global cancer incidence will increase, particularly in developing countries. The estimated 10 million new cancer cases diagnosed world-wide in the year 2000 is predicted to reach at least 15 million by 2020 [8]. By then, the proportion in developing countries will have increased to 70% from the present figure of 60%. Thus, there will be an increasing need for treatment, and for better treatment. One way in which cancer treatment results could be immediately improved and toxic and financial costs reduced, would be the implementation of successful programmes focused on earlier diagnosis. Programmes of this kind should include public education as well as education for non-specialist health care professionals or non-medical personnel who often serve as 'the point of first contact'. Oncologists will also need to be much more involved in the promotion of such efforts. In the meantime, the only available means of reducing the cost of chemotherapy is to give less, or to use less expensive drugs. Should chemotherapy in developing countries be tailored to available resources—physical, human and economic—in those countries? This question will be the focus of the remainder of this article.

Simplifying therapy—realistic or retrogressive?

Although there are exceptions, chemotherapy regimens have tended, over time, to become more complex and more toxic, particularly for patients with advanced disease. Chemotherapy has also been increasingly explored in cancers previously treated by surgery and/or radiotherapy alone. Thus, the affluent nations rightly focus upon whether more patients with advanced disease can be cured by the addition of adjuvant or neoadjuvant chemotherapy, by increasing the intensity of chemotherapy, or by new agents. By contrast, in developing countries, where resources are limited, a case has sometimes been made for giving "simpler" treatment than that recommended in more affluent nations [9]. Even if simpler or less expensive treatments give inferior results, this approach could improve access to care by reducing both costs and toxicity and, paradoxically, might even improve survival rates at a population level. This argument assumes that the results of a particular treatment regimen in developing countries will be the same as in those Western countries in which the efficacy of the regimen was originally documented. However, this is not necessarily so [7], given that tumor, patient and resources may differ markedly. It is least likely to be the case in the poorest populations, which have the worst access to care and the most advanced cancers, yet the greatest need of less expensive regimens. Simplifying therapy in such patients could prove to be disastrous.

Ultimately, rational decisions can be made only on the basis of results of clinical trials conducted in local populations. Every effort should be made to perform such studies, but clinical decisions are usually made in the absence of data from local populations. In this circumstance, and where there is a choice of regimens, it may nevertheless sometimes be appropriate to recommend a less expensive and intensive treatment alternative. The use of adjuvant chemotherapy in early stage breast cancer—uncommon as it is in developing countries—illustrates this issue. The results of a large meta-analysis of randomised trials conducted in affluent countries have shown a statistically significant advantage for anthracycline-containing regimens over cyclophosphamide, methotrexate and 5-fluorouracil (CMF), a regimen developed in the 1970s. However, the difference in survival at 5 years is only 72% versus 69% [10] and the use of anthracyclines is associated with added costs and toxicity. Survival benefits of such adjuvant therapies at 10 years are of the order of 7–11% in women below 50 years in affluent countries and probably only 2–3% in older women. It is not known whether these data apply to a broad range of populations in developing countries, which may be biologically different, or have more advanced disease, even stage for stage. Use of the more expensive and toxic therapy, however, may well lead to a greater depletion of precious resources, and in particularly poor resource settings, to a higher toxic death rate, both of which are likely to outweigh any potential advantage of the anthracycline-containing therapy. Nonetheless, many oncologists in

resource-poor settings base their recommendations on meta-analyses like these, performed on clinical trials that have been conducted in Western populations.

In this context, it is also important to bear in mind that tumour burden or clinical stage is usually a very important determinant of outcome. Careful separation of patients into different prognostic groups, the definition of which may differ in developing countries (another area where local research is greatly needed) [7], is critical. ''Risk-adapted'' therapy must fulfill its function of avoiding unnecessarily toxic and expensive therapy in patients with a lower risk, while clearly identifying those who may be cured using more intensive therapy.

Simpler therapy can be better

Simplification of treatment for all patients may be possible in circumstances where current therapy is more intensive or more complicated than need be—for example, when a regimen containing many drugs is recommended when fewer would suffice, or when expensive high-dose intravenous infusions, or the use of stem cell transplantation are advised in the absence of clear evidence of value. Instances of ''over-treatment'' of this kind may not be common, but more intensive or complex regimens are sometimes adopted in affluent nations without adequate comparison with less intensive approaches. The treatment of osteosarcoma, the use of stem cell transplantation in poor prognosis or advanced breast cancers, or in specific molecular subtypes of acute lymphoblastic leukaemia (ALL) provide examples [11–14]. In these circumstances, simplification of therapy may not reduce survival rates. Indeed, the elimination of treatment elements or drugs that contribute little therapeutic effect, but significant toxicity, may sometimes permit higher or more frequent doses of the more effective drugs with better overall results. Unfortunately, clinical trials comparing reduced-intensity therapy with standard therapy are less popular than trials in which therapy is intensified since the outcome may be worse—as occasionally happens [15]. Exploring the efficacy of simpler therapy may, however, be a more attractive research question in circumstances in which the cost of existing therapies is prohibitive.

Simpler therapy may give also give an improved outcome when intensive, high dose, or complex therapies—or, in the lowest resource settings, even relatively straightforward treatment—require monitoring or supportive care at a level which exceeds the competence of the medical and nursing staff; which requires support facilities or products that are not available; or when intensive therapy exceeds the tolerance of many patients. In such circumstances, the toxic death rate may be so high as to outweigh any advantage that the more intensive therapy might otherwise bring. In these circumstances, simpler therapy should become the treatment of choice.

How long should chemotherapy be continued?

In the context of reducing toxicity and conserving resources, the duration of therapy is probably not given the attention it deserves. Optimal duration is often poorly defined for many diseases. This is, perhaps, particularly the case in paediatric cancers, where the successful model of ALL, in which so-called 'maintenance' therapy is generally continued for some 2 years, has had considerable influence. Other paediatric cancer may still be treated for a year or more, even though a duration of this length may not be necessary. Although attempts to shorten 'maintenance' therapy for ALL have not been successful in the past, it is possible that the duration of therapy for some patients may be reduced without detriment. ''Mature'' B-cell, or L3 ALL—Burkitt's cell leukaemia—for example, often treated with lengthy ALL therapy in the past with poor results, has a much better outcome when treated with a small number of therapy cycles of different design, although excellent results do require quite intensive therapy [16,17]). By the same token, lengthy 'maintenance' therapy may not be necessary for all ALL subtypes—quite different therapeutic strategies may be equally good or better. The molecular profile of ALL, which varies with geography, may have an important bearing on this issue [18].

Although the least therapy consistent with the best results is desirable everywhere, one might conclude that the need to devise simple, short duration therapy is even greater in countries with limited resources than in affluent nations.

The importance of research and education

Simplification of chemotherapy is the most obvious and readily-implemented means of increasing the access of cancer patients in developing countries to treatment, but it must be in the context of the basic problems faced by cancer patients in developing countries, and in particular, their generally more advanced disease. Because developing countries face different problems from affluent countries with respect to the patients, their cancers, and the resources available to treat them, there is an urgent need for more research relevant to these patient populations and treatment facilities. This will require expansion of the present capacity for conducting research, and some restructuring. For example, the roles of paramedical staff might be augmented to help alleviate pressure on doctors. Improving patient education will have a positive effect on compliance and follow-up, while public and non-specialist education will be critical elements in ensuring that patients present much earlier

in the course of their disease. Success in this endeavour would enable a greater number to be treated with simpler therapy and do much to allay the vicious cycle. Conducting more research in developing countries will not only improve the lot of patients in these countries, but should benefit patients everywhere. Science may know no boundaries, but, unfortunately, affluence does. Increased collaboration between rich and poor countries will help to overcome this problem [19], as well as open up new research opportunities in countries which presently carry so much of the global cancer burden.

References

1. Taningher M, Malacarne D, Izzotti A, Ugolini D, Parodi S. Drug metabolism polymorphisms as modulators of cancer susceptibility. *Mutat Res* 1999, **436**, 227–261.
2. Krajinovic M, Labuda D, Sinnett D. Childhood acute lymphoblastic leukemia: genetic determinants of susceptibility and disease outcome. *Rev Environ Health* 2001, **16**, 263–279.
3. Flatt PM, Pietenpol JA. Mechanisms of cell-cycle checkpoints: at the crossroads of carcinogenesis and drug discovery. *Drug Metab Rev* 2000, **32**, 283–305.
4. Advani SH, Banavali SD. Pattern of infection in hematologic malignancies: an Indian experience. *Rev Infect Dis* 1989, **11**(Suppl. 7), S1621–S1628.
5. Odida M, Schmauz R, Lwanga SK. Grade of malignancy of cervical cancer in regions of Uganda with varying malarial endemicity. *Int J Cancer* 2002, **99**, 737–741.
6. Patil AV, Somasundaram KV, Goyal RC. Current health scenario in rural India. *Aust J Rural Health* 2002, **10**, 129–135.
7. Advani S, Pai S, Venzon D, *et al*. Acute lymphoblastic leukemia in India: an analysis of prognostic factors using a single treatment regimen. *Ann Oncol* 1999, **10**, 167–176.
8. Stewart BW, Kleihues P, eds. *World Cancer Report*. Lyon, France, IARC Publications, 2003.
9. Chandy M. Childhood acute lymphoblastic leukemia in India: an approach to management in a three-tier society. *Med Pediatr Oncol* 1995, **25**, 197–203.
10. Early Breast Cancer Trialists' Collaborative Group. Multi-agent chemotherapy for early breast cancer. *Cochrane Database Syst Rev* 2002, **1**, CD000487.
11. Souhami RL, Craft AW, Van der Eijken JW, *et al*. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997, **350**, 911–917.
12. Viens P, Maraninchi D. High-dose chemotherapy in advanced breast cancer. *Crit Rev Oncol Hematol* 2002, **41**, 141–149.
13. Farquhar C, Basser R, Marjoribanks J, *et al*. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer (Cochrane Review). *Cochrane Database Syst Rev* 2003, **1**, CD003139.
14. Pui CH, Gaynon PS, Boyett JM, *et al*. Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet* 2002, **359**, 1909–1915.
15. Schellong G, Bramswig JH, Hornig-Franz I. Treatment of children with Hodgkin's disease—results of the German Pediatric Oncology Group. *Ann Oncol* 1992, **3**(Suppl. 4), 73–76.
16. Ziegler JL. Burkitt's lymphoma. *N Engl J Med* 1981, **305**, 735–745.
17. Magrath IT, Adde M, Shad A, *et al*. Adults and children with small noncleaved cell lymphoma have a similar, excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol* 1996, **14**, 925–934.
18. Inamdar N, Kumar SA, Banavali SD, *et al*. Comparative incidence of the rearrangements of TEL/AML1 and ALL1 genes in pediatric precursor B acute lymphoblastic leukemias in India. *Int J Oncol* 1998, **13**, 1319–1322.
19. Wilimas JA, Ribeiro RC. Pediatric haematology-oncology outreach for developing countries. *Hematol Oncol Clin North Am*, 2001, 775–787.