



## Review

## Prescribing anti-cancer drugs in elderly cancer patients

Silvio Monfardini\*

*Divisione di Oncologia Medica, Azienda Ospedale-Università, Via Giustiniani 2, 35128 Padova, Italy*

Received 1 July 2002; accepted 3 July 2002

## 1. Introduction

Who is old among cancer patients receiving chemotherapy? Seventy years has been considered as the lower limit of senescence [1] since most comorbidities and other age-associated conditions, such as depression and a decrease in physical functions, occur for most people after this age. For many years, most clinical trials in Europe have adopted an upper age limit of 70 years [2], while since the early 1980s in USA, to avoid discrimination of the elderly, this upper age limit for entry into clinical trials has been abolished [3]. As a consequence of these policies, we presently have information, regarding only a few patients older than 70 years that were selected on the basis of their fitness and are quite similar to younger adults.

In recent years, the number of older patients in our wards and clinics has progressively risen. Over 45% of all neoplasia in Europe now occur in patients older than 70 years. Moreover, the pessimistic attitude of relatives and family physicians towards chemotherapy administration has been partially overcome. Dealing with the practical problem of planning chemotherapy in a consistent number of older patients, medical oncologists have progressively understood that the approach to cancer chemotherapy adopted for adults cannot automatically be applied to elderly patients. Empirical drug prescription should be avoided, but data from the results of specific trials for the elderly (even simple phase II studies) is limited. Irrelevant has been the entry of the elderly in phase I studies [4].

Cost is another issue in cancer chemotherapy prescription for the elderly, as it obviously increases, but is probably associated with an inferior cost-effectiveness than in younger adults. Increased costs, time and

resources spent on the older cancer patient as well as compliance to treatment are leading to an increased awareness that before drugs are prescribed, a more accurate assessment of associated diseases is required. In fact, the increased life-span, with the consequent rise in comorbidities, has led to the well known phenomenon of multiple drug prescriptions (polypharmacy) in Europe. In this scenario, drug therapy for cancer in the elderly represents a further burden on the patients but also on the not unlimited resources that are available for health-care in Europe. In this context, and in the best interest of the older cancer patient, we need a better definition of those situations, where active treatment of simple palliation is needed.

Looking forward to the future of cancer chemotherapy in the elderly, an attempt will be made here to envisage possible suggestions for drug prescription.

## 2. Age-associated changes limiting drug prescription

### 2.1. Variations in pharmacokinetics

While age-related changes in pharmacodynamics remain an important area of research, the most important pharmacokinetic parameters may undergo age-related variations as follows.

*Absorption:* may be decreased in the elderly as a result of a number of different changes [5]. With the recent tendency to administer oral drugs in the elderly, attention should be paid to the possible reduced absorption of oral alkylating agents, oral pyrimidines, oral folates and oral etoposide.

*Distribution:* the progressive reduction of total body water, decrease of plasma protein concentration and decrease of haemoglobin, leads to a decreased volume of distribution with consequently increased serum

\* Corresponding author. Tel.: +39-049-8215931; fax: +39-049-8215932.

E-mail address: [silvio.monfardini@unipd.it](mailto:silvio.monfardini@unipd.it) (S. Monfardini).

concentrations and toxicity of taxanes, epidophyllo toxins and anthracyclines. Since these drugs are heavily bound to red blood cells, anaemia, in particular, may precipitate a critical situation [6]. Therefore, the correction of anaemia before and during chemotherapy, is quite important in the older person [1].

*Excretion:* a progressive decline in the glomerular filtration rate is one of the features of aging [7]. A reduced glomerular filtration rate may lead to an enhanced toxicity of drugs excreted by the kidney such as methotrexate, bleomycin and carboplatin, as well as to increased toxicity of the active metabolites that are excreted from the kidneys (anthracyclines, cytarabine at high doses). The Calvert formula is useful to calculate the dose of carboplatin [8], while for the other drugs, the Kintzel and Dorr formula allows the calculation of the dose adjustment with declining renal function [9]. This adjustment is based on the calculation of the fraction of drug or drug metabolite undergoing renal excretion.

*Hepatic metabolism:* age affects mainly type I reactions (p-450 cytochrome enzymes), while type II reactions (glucuronidation) are rarely influenced by age. The clinical consequences of the aging of the liver (including also decreased masses of hepatocytes and decreased blood flow) on chemotherapy administration are not entirely known, but decreased liver function that is associated with aging may lead to an increased toxicity following treatment with drugs that are metabolised by the liver such as cyclophosphamide and ifosfamide, as well as the antimetabolites 5-fluorouracil, cytarabine and gemcitabine [1,10]. Biliary excretion of anthracyclines seems to be unaffected by the age of the patient [11,12].

## 2.2. Reduced stem cell reserve

A limited stem cell reserve in haemopoietic tissues and mucosae may lead to excessive haematological toxicity (leucopenia, thrombocytopenia), as well as to increased mucositis.

While it has been shown that oral toxicity is more frequent in elderly patients, an increased myelotoxicity has not been shown in some retrospective phase II studies probably because of patient selection [2,3], while in others, conducted in non-Hodgkin's lymphomas, an increased haematopoietic toxicity was observed [13–16], as well as the usefulness of prophylactic use of haematopoietic growth factors [17].

## 2.3. Reduced reserve of functional tissue

Enhanced cardiotoxicity and neurotoxicity in the elderly may result in additional tissue injury following chemotherapy. This could be, for example, the case for the cardiotoxicity observed following anthracycline and neurological toxicity following vincristine treatment.

## 2.4. Comorbidity and polypharmacy

The occurrence of chronic comorbidities affects most elderly patients. Comorbidities in a large population of older cancer patients such as cardiovascular diseases, hypertension, chronic bronchial obstruction, diabetes, arthritis, benign prostatic hypertrophy and depression were observed [18] and these were similar to those reported in the general population [19,20]. The likelihood of an older person experiencing a chronic illness increases rapidly with age. The obvious consequence is the concurrent use of several different medications. In fact, it is well known that the elderly are big drug consumers. However, multiple prescriptions are not limited to those given by physicians. Older patients are also often targeted by the mass media with the regard to the promotion of new medications. Health food store personnel, pharmacists, nurses, friends and family members may influence the medication practices of the older patient [21].

How does polypharmacy influence anticancer drug prescription in the older person? Since this issue has never been accurately studied in the oncological arena, a few considerations are worthwhile.

1. The older patient may already present side-effects from other medications to which the side-effects of chemotherapy will be added. These chemotherapy toxic signs may lead to the prescription of other medications (anti-emetics, other supportive therapies).
2. Rates of non-compliance to drugs, in general, have been estimated for the elderly as ranging from 25 to 59% and non-compliance has been more strongly correlated with the number of drugs given than with the age of the patient [22]. It has been reported that 60% of older patients would discontinue a drug without speaking to the physician if the drug does not work [23]. Oral antitumour drugs could therefore result in a low compliance rate as they run the risk of not being taken at all.
3. Adverse drug reactions rise with the addition of new drugs to previous regimens. The administration of antitumour drugs may then increase the number of adverse reactions and result in further problems that need to be considered when phase II studies are planned in these elderly cancer patients.

## 2.5. Other age-associated conditions influencing drug prescription

The ability of an older patient to correctly take the drugs prescribed depends not only on his level of edu-

cation, hearing capacity, visual acuity and memory, but also on his physical condition. For example, these may be patients who are not able to understand the indications of the physician and/or not able to read the tiny writing characters in the instructions for drug use, but also those who are simply not able to walk or drive to the pharmacy.

Due to the heterogeneity of the elderly population, drug prescription in the elderly requires a preliminary evaluation of individual variability in all of these age-associated conditions. Aside from blood chemistry and organ function deficits, all of these limitations can be assessed using a multidimensional geriatric evaluation [18,24,25].

### **3. Choice of drugs to be prescribed (drugs of interest)**

#### *3.1. Which antitumour agents?*

Previously it was thought that the same agents administered to younger adults could be given at empirically-reduced dosages. However, the clinical attitude of medical oncologists caring for patients over 70–75 years is now very different. The few prospective phase II–III single agent studies in older patients have used vinorelbine [26,27], gemcitabine [28] and taxanes [29]. Carboplatin has been largely preferred to cisplatin in the elderly since with the administration of carboplatin based on an area under the curve (AUC), calculation, renal toxicity can be more easily prevented. Furthermore, cisplatin requires a large intravenous (i.v.) fluid administration which may not be comfortable for an older out-patient and contraindicated in older patients who have cardiac decompensation. With these drugs, used alone or in combination, the induction of bone marrow depression has not been considered as a real limiting factor. There is, however, an undeniable reluctance to administer anthracyclines or at least to treat only selected patients, due to the harm of a higher frequency of cardiac toxicity in these older patients. Oral fluoropyrimidines will probably increasingly be used in the elderly, but, at present, very little data are available.

#### *3.2. Single drugs or combination chemotherapy?*

This is not a false dilemma since the present tendency of medical oncologists for older patients, especially for those tumour types in which polychemotherapy does not carry a significant advantage versus monochemotherapy, is to treat with single sequential agents. This has been the case for breast, ovarian, lung non-small carcinoma, and, to some extent, for gastrointestinal (G.I.) malignancies, where single agents are believed to be better tolerated. Obviously this

is not true for the most chemosensitive neoplasia (e.g. malignant lymphomas, small cell lung cancer) where combination chemotherapy still has a leading role to play.

#### *3.3. Oral or intravenous (i.v.) administration?*

The advantage of an i.v. administration is to ensure that a desired amount of drug is given. The obvious disadvantage is the need for the old patient to reach or to be brought to the outpatient clinic or to be admitted to the ward, if prolonged fluid administration is required.

To overcome the discomfort associated with traveling, the oral route has been thought to be an easier, more convenient modality. This is particularly the case if the patient has the capability of drug self-administration without making any mistakes or has somebody who is available to administer the drugs to him/her at home. For patients not having a relative (or somebody else) caring for them in the community, an assessment should be done to determine if this patient is able to take their medication at home. This is apparently an easy task, but in the presence of polypharmacy, as occurs almost unavoidably, compliance and correct use of an anticancer agent may be a big problem.

### **4. Informed consent before prescription**

To our knowledge, informed consent before conventional chemotherapy for elderly cancer patients has not yet been considered to differ from the informed consent of younger patients. However, it has occurred to almost every medical oncologist that it is a difficult question especially in cases where the elderly patients can only partially hear or are totally deaf, where written information is given to old people who cannot read documents that are in small print or can read the information but do not understand its real meaning. Older people may also be too embarrassed to admit that they have not understood and may be ready to sign without understanding what has been proposed. Even more difficult for the elderly, is dealing with research protocols, where usually two different therapies are being tested. This implies at least a perception of understanding the scientific question being asked. The level of scientific knowledge of many elderly people is less than that of the younger generation in Europe and this gap is not going to be filled with a simple conversation with the medical oncologist and/or written information sent to the family physician. In some cases, the consent may come from the relatives accompanying the patient. If the family agrees, the green light will also be given by the patient. But is this a real consensus? Should we seek for more awareness on behalf of the

patient? Sometimes in self-sufficient patients who are totally caring for themselves this may be possible. This, however, is not the rule, but rather the exception. Controlled randomised trials on cancer chemotherapy are needed, but the barrier of inadequate information and comprehension of the consent mechanism needs to be overcome.

## 5. The cost of prescription

Anticancer drug administration in the elderly is less cost-effective than in young adults, probably due to the smaller gain in survival obtained and increased risk of complications requiring further expensive treatment [30]. Clearly this increase in costs should not be a reason to restrict drug prescription in older patients, but rather to develop guidelines taking into account whether the patient needs active treatment or simple palliation and then also the cost of drugs. It has been underlined that there is a cost also associated with not treating cancer, due to the expense of treating the symptoms, and that this cost could be even greater than that of the chemotherapy administration [1]. This assumption, however, has never been proven.

Concerning the use of haematopoietic growth factors, there is agreement, at least in the USA, that these should be used prophylactically if moderate intensity chemotherapy (e.g. cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is administered [31]. This will increase the drug expense, but decrease the costs for hospitalisation for sepsis from neutropenic fever. Since anaemia should be corrected in the elderly in order to increase the tolerance to chemotherapy [1] erythropoietin has a definite, if not yet well established, role. With regard then to the other most expensive monoclonal antibodies, Rituximab has been shown to be effective in older patients with non-Hodgkin's lymphomas together with CHOP treatment [32], while Trastuzumab, in view of the possible cardiac toxicity, should probably still not be prescribed in women over 70 years of age with advanced breast cancer.

## 6. Prescriptions in frail patients

Patients aged more than 80–85 years or over 70 years, but with severe comorbidity or with geriatric syndromes (dementia, delirium, depression, incontinence, more than 2 falls in a month, failure to thrive, severe comorbidity, or inability to care for themselves) and advanced cancer need a different (even if not yet well defined) approach to drug prescription. Simple pharmacological palliation of symptoms may be an option. If the circumstances are such that the decision of administering chemotherapy is taken, single agents would be the best

choice in most solid tumour types, but probably not for non-Hodgkin's lymphomas and acute myeloid leukaemia (AML), among the most frequent haematological neoplasia in the elderly [33]. In general, the i.v. route is preferable in these patients.

## 7. Outlooks for the future

Drug prescription in the elderly is a complex process which needs to be improved, facilitated and somewhat simplified for the future.

Since drug tolerance and compliance in the elderly may be reduced, we need to develop new, less toxic, but nevertheless, active agents. Some examples, such as the monoclonal antibody rituximab, are already at hand [33]. But even among the chemotherapeutic agents, some of them, such as vinorelbine and gemcitabine, are potential compounds for the future. New protective agents besides cardioxane and amifostine [34,35] will probably also be developed. A more widespread use of haematopoietic growth factors will, hopefully, be possible at a lower cost.

To reach these targets, new drug development programmes should also include elderly patients. Phase I and II studies should be conducted in patients ranging from 70 to 80 years of age without major comorbidities, with minor physical function impairment and without mental deterioration. Of course, the results of these studies conducted in relatively homogeneous populations will then have to be applied taking into consideration the heterogeneity of the elderly population, but at least a common starting background will be available. To improve anticancer drug development, phase III studies including the elderly will also be necessary, but a new methodology will have to be thought out, because of the same problem of heterogeneity and, therefore, of comparability of the two different patient populations.

But in running the necessary and the specifically oriented clinical trials, the lay out of new and specific consent forms will have to be improved. Even small modifications (e.g. magnification of the written characters) will be of use. Alternatively, consent forms for the family could be developed.

Drug prescription will require the assessment of more subtle and sophisticated biochemical and/or molecular tests in order to understand in advance which patients are at risk of organ failure and rule out those with a foreseen excessive renal, liver or lung toxicity.

To avoid adverse events, derived from the interaction of anticancer agents with the pre-existent multiple medications, a closer contact with the clinical pharmacologist will prove useful, since medical oncologists know quite well the pharmacology of anticancer drugs, but to a lesser extent that of other drugs.

In order to optimally prescribe, we have to understand in a more professional way if the old man or woman will be able to take the drugs without confusing them with the “old drugs” he or she is already taking. To determine their visual acuity, hearing capability and understanding of the meaning and side-effects of drug administration in general is quite important. This assessment can be performed using the multidimensional geriatric evaluation [25]. However, the use of this tool is a recommendation for the future, since at present only a few medical oncologists are convinced of its usefulness, as it is thought to be too time-consuming and not yet of obvious and demonstrated usefulness. However, in the future, a simple screening should be available to determine which patients need to be assessed with the multidimensional geriatric evaluation and which do not. Furthermore, a very simplified version to be used before drug prescription is likely to be prepared.

To make i.v. regimens easier to administer, home delivery of anti-cancer drugs could be organised and the drug could be given in the home environment.

Should this be done now, it will mean a definite increase in costs. However, in the near future, with a better refinement of geriatric nursing procedures, this solution will probably prove to be more comfortable for the patient and not that much more expensive.

To improve cancer chemotherapy administration in the elderly, in the United States in 2001 nearly 19 million of US dollars have been provided to medical institutions to develop combined programmes in medical oncology and geriatric medicine through the auspices of the American Society of Clinical Oncology (ASCO). With the creation of this combined programme in geriatric oncology, enrolled fellows will become eligible for a certification in Medical Oncology with an added qualification in geriatric medicine in just 3 years. This will also allow the further development of clinical trials that are specific for elderly patients. With these goals in mind, a training programme for geriatric oncology also needs to be set up in the European Community, if we are to meet the challenges ahead.

## Acknowledgements

The author thanks Mrs Loredana Casagrande and Dr Federica Vascon for the assistance in the preparation of the manuscript. Supported by the Centro Oncologico Regionale (COR) Padova.

## References

- Balducci L. Geriatric oncology: challenges for the new century. *Eur J Cancer* 2000, **36**, 1741–1754.
- Monfardini S, Sorio R, Hocht Boes G. Entry and evaluation of elderly patients in European Organization for Research and Treatment of Cancer (EORTC) new drug development studies. *Cancer* 1995, **76**, 333–338.
- Begg CB, Carbone PP. Clinical trials and drug toxicity in the elderly: the experience of the Eastern Cooperative Oncology Group. *Cancer* 1983, **52**, 1986–1992.
- Monfardini S, Sorio R, Kaye S. Should elderly cancer patients be entered in dose escalation studies? *Ann Oncol* 1994, **5**, 964–966.
- Iber FL, Murphy PA, Connor ES. Age-related changes in the gastrointestinal system. *Drugs and Aging* 1994, **5**, 34–48.
- Pierelli L, Perillo A, Greggi S, et al. Erythropoietin addition to granulocyte-colony stimulating factor abrogates life-threatening neutropenia and increases peripheral blood progenitor-cell mobilization after epirubicin, paclitaxel and cisplatin in combination chemotherapy. *J Clin Oncol* 1999, **17**, 1288–1296.
- Anderson S, Brenner BM. Effects of aging on the renal glomerulus. *Am J Med* 1986, **80**, 435–442.
- Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989, **7**, 1748–1756.
- Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev* 1995, **21**, 33–64.
- Cova D, Beretta G, Balducci L. Cancer chemotherapy in the older patient. In Balducci L, ed. *Comprehensive Geriatric Oncology*. Harwood Acad. Publ., 1998, 429–442.
- Robert J, Hoerni B. Age dependence of the early phase pharmacokinetics of doxorubicin. *Cancer Res* 1983, **43**, 4467.
- Egorin MJ, Zuhowsky EG, Thompson B, et al. Age related alteration in daunorubicin pharmacokinetics. *Proc Am Soc Clin Oncol* 1987, **6**, 38.
- Tirelli U, Errante D, Van Glabbeke M, et al. COHP is the standard regimen in patients > 70 years of age with intermediate and high grade non Hodgkin's lymphoma: results of a randomized study of the European Organization for the Research and Treatment of Cancer lymphoma cooperative study. *J Clin Oncol* 1998, **16**, 27–43.
- Bastion Y, Blay J-Y, Divine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation response to treatment and survival. A group d'Etude de Lymphomes de l'Adulte Study on 453 patients older than 70 years. *J Clin Oncol* 1997, **15**, 2945–2953.
- Gomez H, Mas L, Casanova L, et al. Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: identification of two age subgroup with differing hematologic toxicity. *J Clin Oncol* 1998, **16**, 2352–2358.
- Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP vs CNOP chemotherapy. *J Clin Oncol* 1995, **13**, 2530–2539.
- Zinzani PG, Storti S, Zaccaria A, et al. Elderly aggressive histology non-Hodgkin's lymphoma: first line VNCOP-B regimen: experience on 350 patients. *Blood* 1999, **94**, 33–38.
- Repetto L, Fratino L, Audisio R, et al. Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an italian group for geriatric oncology study. *J Clin Oncol* 2002, **20**, 494–502.
- Yancik R, Havlik RJ, Wesley MN, et al. Cancer and comorbidity in older patients: a descriptive profile. *Ann Epidemiol* 1996, **6**, 399–412.
- Bergman L, Dekker G, Van Kerkhoff EHM, et al. Influence of age and comorbidity on treatment choice and survival in elderly patients. *Breast Cancer Res Treat* 1991, **18**, 189–198.

21. Corcoran ME. Polypharmacy in the older patients. In Balducci L, ed. *Comprehensive Geriatric Oncology*. Harwood Acad. Publ., 1998, 525–532.
22. Col N, Fanale JE, Kroholm P. The role of medication non-compliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990, **150**, 841–845.
23. Gebhart MW, Governali JF, Hart EJ. : Drug related behavior, knowledge and misconceptions among a selected group of senior citizen. *J Drug Educ* 1978, **8**, 85–92.
24. Monfardini S, Ferrucci L, Fratino L, *et al.* Validation of a multidimensional evaluation scale for use in elderly cancer patients. *Cancer* 1996, **77**, 395–401.
25. Monfardini S, Balducci L. A comprehensive geriatric assessment (GGA) is necessary for the study and the management of cancer in the elderly. *Eur J Cancer* 1999, **35**, 1771–1772.
26. Sorio R, Robieux I, Galligioni E, *et al.* Short communication, pharmacokinetics and tolerance of vinorelbine in elderly patients with metastatic breast cancer. *Eur J Cancer* 1997, **33**, 301–303.
27. Gridelli C, Perrone F, Gallo C, *et al.* On the behalf of ELVIS Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J Natl Cancer Inst* 1999, **91**, 66–92.
28. Altavilla G, Adamo V, Buemi B, *et al.* Gemcitabine as single agent in the treatment of elderly patients with advanced non-small cell lung cancer. *Anticancer Res* 2000, **20**, 3675–3678.
29. Hainsworth JD, Burris HA, Yardley DA, *et al.* Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *Clin Oncol* 2001, **19**, 3500–3505.
30. Zagonel V, Fratino L, Ferrucci L. Therapeutic choice with regard to life expectancy and cost benefit analysis in cancer diagnosis and treatment. *Crit Rev Oncol Hematol* 1998, **27**, 121–123.
31. Balducci L, Yates G. Proposed guideline for the management of the older person with cancer. *Oncology* (in press).
32. Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New Engl J* 2002, **346**, 235–241.
33. Lowenberg B, Zittoun R, Kerkhofs H, *et al.* On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *J Clin Oncol* 1989, **7**, 1268–1274.
34. Koning J, Palmer P, Franks CR, *et al.* Cardioxane-ICRF-187 Towards anticancer drug specificity through selective toxicity reduction. *Cancer Treat Rev* 1991, **18**, 1–19.
35. Glover DJ, Glick JH, Weiler C, *et al.* WR-2721 and high dose cisplatin. An active combination in the treatment of metastatic melanoma. *J Clin Oncol* 1987, **5**, 574–578.