Chapter 12

GUIDELINES FOR THE MANAGEMENT OF THE OLDER CANCER PATIENT

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Age may influence the management of cancer in the older person in at least three areas: evaluation of the patient, increased risk of treatment complications, and changes in the biology of common tumors. The assessment of the patient involves, in addition to an estimate of life expectancy and risk of treatment complications, recognition of reversible conditions that may compromise the safety and efficacy of treatment, the patient's function and quality of life. These may include comorbidity, mild dementia, depression, anemia, and lack of adequate social support [1]. Age is also associated with increased risk of certain therapeutic complications, such as mielodepression, mucositis, neuro and cardiotoxicity following cytotoxic chemotherapy [2]. It is well recognized that the prognosis of different tumors may change with age. For example, acute myeloid leukemia and non – Hodgkin's lymphomas may become more resistant to chemotherapy, whereas the course of breast cancer may become more indolent.

The recognition that age may influence the management of cancer prompted a number of organizations to issue guidelines for the management of older individuals with cancer. The National Cancer Center Network (NCCN) and the European Organization for the Research and Treatment of Cancer (EORTC) have published a detailed set of guidelines addressing the issues of the elderly (Table 1) [3, 4]. In addition the American Society of Clinical Oncology (ASCO) has inserted age-related provisions in the

Table 1. Management Guidelines

NCCN Guidelines related to the management of older cancer patients

- All cancer patients aged 70 and older should undergo some form of geriatric assessment
- Colony-stimulating factors should be use to support prophylactically persons aged 65 and over receiving moderately toxic chemotherapy (CHOP, CA)
- Patient's hemoglobin should be kept at 12 gm/dl or higher with erythropoietin
- Doses of chemotherapy should be adjusted to the renal function of patients aged 65+
- Capecitabine should be used "in lieu " of intravenous fluorinated pyrimidines, when feasible
- Acute myelogenous leukemia in patients aged 70 + should be managed in a cancer center

EORTC Guidelines

- Prophylactic filgrastim in elderly patients with non-Hodgkin's lymphoma, small cell lung cancer, and urothelial tumors [4]

recommendations for the use of hemopoietic growth factors [5]. This chapter reviews the evidence that justifies existing guidelines[6] and highlight areas in which more information is wanted.

1. GUIDELINES: PRINCIPALS AND GOALS

The goals of guidelines for the diagnosis and management of diseases include [6]:

- A simple and uniform approach to the practice of medicine, comprehensive of relevant new information. To this end, the guidelines need two attributes: accessibility and plasticity.
- A framework of reference for quality assurance of medicine, nursing and health allied profession;
- Analysis of the levels of evidence that support current approach to disease. This is basilar to identify areas in which more information is necessary and urgent and to prioritize ongoing research. The level of evidence is classified according to the criteria of the United States Preventive Service Task Force [7,8] (Table 2). At this point it is useful to underline that the goal of the guidelines is to promote the acquisition of new and better evidence in areas of uncertainty, not to discourage time-honored successful practices, such as appendectomy

for acute appendicitis, that have resulted in reduction of mortality and morbidity, even if they were developed before the definition of the rules of evidence.

Not unique of, but germane to, geriatric oncology is the definition of the adequate management end-points. The most desirable end-points of any diagnostic and treatment intervention are a reduction in mortality and a prolongation of survival. In the case of older individuals, with limited life expectancy, preservation of function and quality of life may be considered alternative end-point. In the following discussion, when appropriate, the effectiveness of an intervention will be assessed according to these end-points as well.

2. ASSESSMENT OF THE OLDER CANCER PATIENT

The NCCN recommends that individuals aged 70 and older undergo some forms of geriatric assessment [3], while the EORTC does not afford the issue. The potential benefits of the geriatric assessment include:

- Estimate of life-expectancy and tolerance of chemotherapy
- Recognition and management of conditions that may interfere with the treatment of cancer
- Adoption of a common language in the description of older patients, that may be used to interpret retrospective treatment analysis and to enroll patients in prospective clinical trials
- Preservation of function and reduction of hospitalization

The NCCN does not recommend a specific form of geriatric assessment. It recognizes that a comprehensive geriatric assessment (CGA) may not be feasible in a busy oncology practice and suggests that some form of screening be adopted to identify subjects in need of a more comprehensive evaluation. These recommendations take into account that a number of different instruments have been developed, including questionnaires, tests of physical performance and even laboratory tests, that may provide rapid and reliable information.

2.1 Evidence Supporting the Recommendation

2.1.1 Estimate of Life Expectancy and Treatment Tolerance

A number of cohort studies have demonstrated that functional deterioration, [9-13], cognitive decline [14-17], depression [18-22], comorbidity [24-26], and some geriatric syndromes, including falls [27], incontinence [28], delirium [29], failure to thrive [30], and neglect and abuse [31-33], are all associated with increased mortality (quality of evidence 2a). Though an interaction exists

Table 2. Levels of evidence

I.	Based on two or more randomized controlled clinical trials
IIa.	Based on one randomized clinical trial or on well done cohort studies
IIb.	Based on retrospective clinical studies
IIc.	Based on personal experience or anecdotic reports
IId.	Based on authoritative opinion
III.	No supportive evidence whatsoever

among functional and cognitive decline and comorbidity [34], a comprehensive index predicting the risk of mortality based on these different parameters is still wanted. The most practical application of the geriatric assessment to the prediction of life expectancy may involve the life-table methods, for long-term life expectancy (Table 3) [13]; whereas the formula of Walter et al may be used to predict short-term (one-year) mortality (Table 4) [9].

Patients who are dependent in ADLs, or who present one or more geriatric syndromes, or who have some serious forms of comorbidity fall in the lower quartile of life expectancy, those who are fully independent and with negligible comorbidity in the upper quartile, and those between these two situations in the intermediate quartiles.

2.1.2 Prediction of Chemotherapy-Related Toxicity

Two cohort studies of older cancer patients demonstrated that dependence in IADL was an independent risk factor for myelotoxicity in patients treated with moderately toxic chemotherapy [36, 37] (quality of evidence 2A). It is reasonable to recommend that both performance status and degree of functional dependence be assessed in older patients as they appear as independent variables [38].

2.1.3 Recognition of Conditions that May Interfere with Cancer Treatment and are Potentially Reversible

This claim is supported by three cohort studies (quality of evidence 2A). Of 200 patients treated in the Senior Adult Oncology Program (SAOP) at the H. Lee Moffitt Cancer Center in Tampa, who had undergone CGA at the time of the initial visit approximately 70% had severe comorbidity; 20% presented

Table 3. Life table assessment of life expectancy. Each age group is divided in quartiles of average life expectancy in years. The geriatric assessment suggests in which quartile is found each individual.

Men

Age	70	75	80	85	90
Upper quartile	18	14.2	10.8	7.9	4.3
Intermediate quartiles	12.4	9.3	6.7	4.7	2.3
Lower quartile	6.7	4.9	3.3	2.2	1

Women

Age	70	75	80	85	90
Upper quartile	21.3	17	10.8	7.9	4.3
Intermediate quartiles	15.7	11.9	6.7	3.2	2.3
Lower quartile	9.5	6.8	3.3	1.5	1

malnutrition, depression, and dementia 70% were dependent in ADL, 70% in IADL and 50% had polypharmacy [38]. The majority of these findings would have been missed without the CGA. Similar findings were recently reported by Repetto et al among Italian patients aged 65 and over [39], and by Ingram et al among Veterans aged 65 and over treated for cancer at the Durham VA Medical Center [40]. None of the studies reported the number of cases in which inadequate social support was detected. This benefit of the geriatric assessment emerged from a pilot study by Extermann et al involving 15 women aged 70 and older with early stage breast cancer. Almost 50% of these patients lacked an adequate caregiver able to support them during the administration of adjuvant treatment [41].

2.1.4 Preservation of Functional Independence and Quality of Life

A number of randomized controlled studies have demonstrated that a CGA leads to reduced hospitalization rate, and reduced rate of admission to assisted living facility in the general geriatric population (quality of evidence 1) [42-50]. It is controversial whether the performance of a CGA does lead also

Table 4. Prediction of one-year mortality following hospitalization, according to Walter [13].

A. Scores for each variable

Risk factor	Point
Male sex	1
Function: 1-4 ADL all ADL	 2 5
Comorbidity Congestive heart failure Solitary cancer Metastatic cancer Creatinine > 3 mg/dl	 2 3 8 2
Albumin 3.0-3.4 gm/dl < 3.0 gm/dl	 1 2

B. Total score and risk of one-year mortality

Total Score	1-year mortality
0-1	13%
2-3	20%
4-6	37%
> 6	68%

to reduced mortality rate [42,51-54]. While no data specific for older persons with cancer are available, it is reasonable to infer that the CGA may be beneficial to all older individuals including those with cancer.

Table 5. Taxonomy of age (modified from Hamerman [34])

Type	Description	Rehabilitative needs
Primary	Fully independent Negligible Comorbidity	Health and Function Maintenance
Intermediate	• May be dependent in one or more IADL • < 3 comorbid conditions; intermediate comorbidity scores	May be rehabilitated to some extent
Secondary or frailty	Classical definition: one or more of the following: • ADL dependence • ≥ 1 geriatric syndrome • ≥ 3 comorbid conditions Alternate definition: at least three of the following: • unintentional weight loss ≥ 10% original body weight over one year; • self-reported exhaustion • decreased grip strength • slow movements • Difficulty in initiating movements	Prevention of further functional deterioration
Near death	Life-expectancy ≥ 3 months; no treatment available	No rehabilitation

2.1.5 Adoption of a Common Language in the Classification of Older Individuals Receiving Cancer Treatment or Entering Clinical Trials of Cancer Treatment

Clearly, the CGA assessment provides elements of common language, such as functional dependence, geriatric syndromes, polypharmacy, etc. These elements have not been integrated yet in a common and accepted language. Two types of approaches to the construction of such language are currently undertaken. One approach consists in subdividing older individuals into groups of different life expectancies and tolerance of treatment. Such taxonomy of aging was first proposed by Hamerman who recognized four states of aging [55] (Table 5). This classification reflects to some extent the cohort study by Rockwood et al,

who demonstrated different life expectancies according to functional status and presence of one or more geriatric syndrome [28]. The main advantage of this approach is its simplicity. The main disadvantage is two fold: The definition of frailty is controversial[56, 57] and so is its reversibility. For some authors frailty represent an exhaustion of functional reserve [56], whereas for other authors it represent a critical reduction thereof that makes older individuals more vulnerable to stress [57-62]. Furthermore, even advanced stages of frailty may be reversible to some extent [63]. Second, the intermediate group of individuals is too vaguely defined and encompasses too large a gamut of conditions to be helpful in treatment-related decisions. Nevertheless, Hamerman's taxonomy has the merit to provide a frame of reference for a physiologic rather than chronologic classification of aging [55]. The other approach consists in the formulation of a comprehensive index of vulnerability capable to predict exactly the risk of death, functional decline, and therapeutic complications [58]. An example of this index is the so-called CRASH index (chemotherapy-related susceptibility high age adults) proposed by Extermann et al, which integrates both chemotherapy-related and patient-related elements.[64].

2.2 Evolution of the Geriatric Assessment

In its present forms, the geriatric assessment presents two problems: it is time-consuming and produces data that are in part subjective. Ongoing research efforts are aimed to make the geriatric assessment more user-friendly and more objective.

2.2.1 Screening Tests to Recognize Patients at Risk of Death and Functional Decline

Screening test to recognize patients who may benefit of a more "in depth" assessment include screening questionnaires, and tests of physical performance. To minimize the time investment of the geriatric assessment in a busy oncology practice, the NCCN has proposed that all patients be screened with the instrument of Lachs, a 14 item questionnaire with a sensitivity for CGA abnormalities of approximately 70% [3, 65] Other instruments, developed since the issuance of the guidelines may prove more appropriate. Examples of these instruments include the Vulnerable Elderly Survey 13 (VES 13), a 13 item questionnaire (Table 6) [58] capable to predict death and functional dependence, and a self-reported lengthy questionnaire including function, comorbidiry, emotional and social resources whose feasibility was described by Ingram et al in more than 500 Veterans with cancer studied at the Durham VA Hospital [40]. These new findings illustrate

Table 6. Vulnerability

A. Vulnerability scale

Element of assessment	Score
Age	
• 75-84	1
• ≥ 85	3
Self-reported health	
• Good or excellent	0
• Fair or poor	1
ADL/IADL. Needs helps in	
• Shopping	1
• Money management	1
• Light housework	1
• Transferring	1
• Bathing	1
Activities. Needs help in	
•STOOPING, CROUCHING OR KNEELING	1
•LIFTING OR CARRYING 10LBS	1
•WRITING OF HANDLING SMALL OBJECTS	1
•REACHING OR EXTENDING ARM ABOVE SHOULDER	1
•WALKING 1/4 MILE	1
•HEAVY HOUSEWORK	1

B. Vulnerability scores, functional decline and survival

Score	Risk of functional decline or death
1-2	11.8%
3+	49.8%
1-3	14.8%
4+	54.9%

the evolution of the geriatric assessment and the new opportunity that may become available for a more efficient and meaningful testing.

A number of physical performance tests predict the risk of disability, functional decline and death [66-71]. Some of these tests may reasonably be used to identify older individuals in need of a complete CGA. Two tests of physical performance appear particularly promising: the "arm chair" test and the seven-item test [70, 71]. The armchair test consists of asking a person to get

up from an armchair, walk ten feet and come back. The score includes: one point for using the arms of the chair to get up, one point for taking more than a second for completing the task, and one point for uncertain gait. The final score can vary from 0 to 3: the higher the score, the higher the risk of death and functional dependence. The seven-item performance test involves the performance of seven simple tasks and is scored according to the easiness by which each task is performed. Terret et al determined that this test was more sensitive than performance status in identifying abnormalities of the CGA in older patients with cancer [71].

2.2.2 Laboratory Assessment of Aging

A number of potential biochemical markers of aging have been described. Aging may be construed as the result of successive inflammatory episodes that lead to an accumulation of catabolic cytokines in the circulation. In addition to favor catabolism, these cytokines may activate the clotting cascade. The validity of this construct was proven by a recent study of Cohen et al [60]. These authors demonstrated that in home-dwelling individuals aged 70 and over, an increased concentration of Interleukin 6 or of D-Dimer in the circulation predicted an increment of 40-60% in risk of mortality or functional dependence in two years. When the concentration of both substances was increased, the increment in risk was 150%. For a long time, it has been known that the concentration of Interleukin 6 (IL-6) is increased in a number of aging-related conditions, from osteoporosis to Alzheimer dementia [59, 72, 73], and IL-6 has been considered a biomarker of aging. These laboratory findings suggest that measurement of circulating levels of IL-6 and possibly of other cytokines, whose concentration is associated with neurodegenerative disorders typical of aging should be included in future studies of geriatric assessment. The value of the laboratory in the clinical assessment of aging is unestablished.

2.2.3 Conclusive Recommendations

Some form of geriatric assessment is clearly beneficial to the management of older individuals with cancer. It appears reasonable to screen individuals aged 70+ with a short questionnaire of with some simple tests of physical performance and to execute a full assessment in individuals at risk. The value of laboratory tests and the most cost-effective screening test will be established in future studies.

2.3 Treatment-Related Recommendations

2.3.1 Dose-Adjustment According to the Glomerular Filtration Rate (GFR) in Persons Aged 65 and Older

This recommendation is based on the following findings:

- The GFR undergoes a decline in the majority of people aged 65 and older [74].
- The adjustment of the dose of methotrexate and cyclophosphamide to the GFR in women aged 65 and over with metastatic breast cancer reduced the toxicity but not the effectiveness of chemotherapy [75].
- This recommendation is fraught with a number of difficulties including the fact that the AUC of a drug is unpredictable to large extent and is at least in part dependent on pharmacogenomic [76]. The determination of the GFR is problematic: direct measurement with radioactive hippurate is not practical; and the 24-hour urine collection for the determination of the creatinine clearance is seldom accurate. The most popular measurement of the GFR include the use of formula accounting for the subject's age, sex, and serum creatinine, but this formula imply a similar decline in GFR and muscular mass in all subjects [77, 78]. Another difficulty involves the calculation of the excretion of active drug metabolites, such as idarubicinol and daunorubicinol, that account for most of the activity of the parent compound [79].
- It may be advisable to adjust the first dose of chemotherapy in individuals aged 65 and over, as long as the dose is escalated during the following cycles of chemotherapy if no toxicity is seen.

2.3.2 Use of Colony Stimulating Factors After Age 65, for Patients Receiving Moderately Toxic Chemotherapy (CHOP, CA)

This recommendation is based on multiple pieces of evidence:

- The risk of neutropenia and neutropenic infections increased after age 65 and older in the experience of three major cooperative groups: the South West Oncology Group (SWOG) [80], the Eastern Cooperative Oncology Group (ECOG) [81] and in the International Breast Cancer Study Group (IBCSG) [82] (level 2B evidence).
- In eight prospective studies of treatment of lymphoma with CHOP or CHOP like combination chemotherapy, in older patients the rate of grade iv neutropenia was consistently higher than 50%, the risk of neutropenic infections varied between 20-47% and the risk of infectious death between 5-15%, with one exception (Table 7) [83-90]. The lower patient age was 60, 65 or 70 in different studies. The

single exception to these findings was the study of Dijurdijn et al, where patients aged 65 and over were randomized to receive prophylactic G-CSF or no G-CSF. The study was well balanced in terms of age and comorbidity between the two groups of patients; however, patients randomized to G-CSF had more advanced local disease that may imply a worse prognosis [91]. Of special interest was the finding that during the first course of treatment the infection rate was much higher among the people not receiving G-CSF (32% vs 20%). The decline of infections in the following cycles may be explained by the fact that the immune defenses were restored among patients who obtained a remission of their disease, but also by the fact that most patients susceptible to infection had been eliminated from the study. The drop out rate due to infectious complications was twice as high among individuals who had not received G-CSF. Other reasons of concerns were the fact that the five year survival in both group of patients was lower than in other studies, and the infection rate was much lower both than the experience of other studies and than the North American practice experience [92]. For this reason, the NCCN has decided not to change its recommendations on account of this study.

- The demonstration by Dees et al in a small number of breast cancer patients that myelotoxicity from doxorubicin cyclophosphamide was cumulative for women aged 65 and older but not for those younger [93].
- The demonstration that filgrastim appear as active in individuals aged 70 and older as it is in younger individuals [83, 88, 91, 94-96].
- Economic considerations. Lyman et al showed that threshold risk of neutropenic infections beyond which neutropenia prophylaxis with filgrastim was cost-effective was around 20% [97], which is the case in all lymphoma studies involving individuals over 60. The threshold may even be lower for these individuals as the duration of their hospitalization is 25% longer than for the young ones [98].
- Alternative strategies to ameliorate the risk of infectious complications may not seem to work as well. Dose reduction has consistently resulted in poorer outcome [84-86, 88, 99, 100]. This finding was supported by the report of the German Lymphoma Study Group demonstrating that CHOP every two weeks in individuals aged 60-75 resulted in higher response rate and survival than standard three weekly CHOP [101]. The effectiveness of another strategy, the use of prophylactic oral antibiotics has not been proven in randomized controlled trials in the elderly [102].

In the case of acute myelogenous leukemia colony stimulating factors may improve the patient survival [103-105] and definitely reduce

Table 7. Myelodepression in elderly patients treated with a CHOP-like chemotherapy combination.

Author (s)	Patient #	Regimen	Age	Neutro-penia	Neutro-penic Fever	Treat-ment related Deaths
Zinzani (83)	161	VNCOP-B	60+	44%	32%	1.3%
Sonneveld (84)	148	CHOP CNOP	60+ 60+	NR NR	NR NR	14% 13%
Gomez (85)	249	CHOP	60+ 70+	24% 73%	8% 42%	0 20%
Tirelli (86)	119	VMP CHOP	70 + 70+	50% 48%	21% 21%	7% 5%
Bastion (87)	444	CVP CTVP	70+ 70+	9% 29%	7% 13%	12% 15%
Osby (88)						
O'Reilly (89)	63	POCE	65+	50%	20%	8%
Coiffier (90)	399	CHOP CHOP-Rituxan	60+	NR	12-20%	5%
Doorjidin (91)	374	CHOP	65+	-	32% (first course)	4%

- the duration of hospitalization for neutropenic infections (Level 1 evidence) [106].

Two major international organizations have recently issued similar recommendations. The American Society of Clinical Oncology recommended that individual aged 65 and older be treated with prophylactic filgrastim or pegrilgrastim when receiving moderately toxic chemotherapy [5]. The EORTC recommended that filgrastim be used prophylactically in patients aged 70 and older receiving adjuvant chemotherapy for breast cancer or treatment with CHOP and CHOP-like regimens for non-Hodgkin's lymphoma [4].

The prophylactic use of filgrastim or pegfilgrastim appears at present as the most prudent and cost-effective course of action for individuals aged 65-70 and over receiving moderately toxic chemotherapy regimens. In the case of large cell lymphoma and the adjuvant treatment of breast cancer this recommendation may appear even more advisable by he suggestion that dose dense treatment may improve the outcome of these patients [101]. Also in the

case of lymphoma, the addition of Rituximab to the CHOP regimens, as supported be two large clinical trials [90], may enhance the risk of mielodepression.

A number of issues emerged from clinical trials may change this approach in the future and should be recognized and addressed. Perhaps the most important is the issue of cost. The basic assumption of the decision analysis of Lyman was that all episodes of neutropenic infections warranted hospital admission [97]. That policy has evolved in the USA. At present hospital admission is not warranted anymore in the absence of sepsis, liver or kidney disfunction, or pneumonia [107]. These patients may be treated as oral antibiotics as outpatients with a significant reduction of cost. Even for those who need intravenous antibiotics, the administration of these medications may occur in the outpatient setting. The study by Doordijin et al [91] suggested that the main benefit of filgrastim for older individuals treated with CHOP was a reduction in these minor infections and in the use of oral antibiotics. An analysis of all lymphoma trials in elderly individuals by Korourkis et al suggested that performance status rather than age was the main risk factor for neutropenic infections and the prophylactic use of growth factors may be limited to these individuals. Other issues of interest include the effects of growth factors on quality of life, survival, quality of life adjusted survival, and function [108].

2.3.3 Maintenance of Hemoglobin Levels ≥ 12 gm/dl with Erythropoietin

In cancer patients, the main basis of this recommendation was the increased risk of myelotoxicity associated with anemia during treatment with anthracyclines, alkaloids, épipodophyllotoxines, and camptothecins (level 2b evidence) [36, 109-113], and the increased risk of functional dependence [114-117] which is of special concerns to older individuals, more vulnerable to this complication.

This recommendation is also supported by other findings, including:

- Anemia as an independent risk factor for mortality in elderly patients [115,118-120] reported in three retrospective [118-120] and one cohort study [115].
- Anemia as a risk factor for decreased response and survival among patients receiving radiation therapy for cancer of the cervix and of the head and neck [121, 122].
- The demonstration that the highest incremental improvement in fatigue is seen when hemoglobin levels raise from 11 to 13 gm/dl [123, 124]. To this it should be added that among elderly patients the prevalence of functional independence increases in parallel with

hemoglobin levels, even within ranges of hemoglobin levels that are considered normal [115, 116, 121].

- The association of chronic anemia with coronary death, congestive heart failure and memory disorders [125-128].

2.3.4 Substitution of Intravenous Fluorinated Pyrimidines with Capecitabine

This recommendation stems from the increased incidence of mucosal toxicity from fluorinated pyriminine in older individuals, well documented in two retrospective studies (level of evidence 2c). In favor of capecitabine are:

- Two randomized controlled studies comparing capecitabine to intravenous fluorouracil in cancer of large bowel, reporting a substantial reduction in the risk of mucositis [129]. This finding could be expected, as capecitabine is a prodrug activated mainly in the liver and in the neoplastic tissue: consequently, the exposure of normal tissues to the active principle is minimized [129].
- The oral formulation allows a major flexibility in dosage

At present there is not enough evidence to extend this recommendation to other oral preparation of fluorinated pyrimidines. It should be remembered that the dose of capecitabine should be adjusted to the glomerular filtration rate that is commonly reduced in older individuals.

2.3.5 Management of Individual Tumors

The NCCN recommended that the management of individual tumors in the elderly is best trusted to the committees charged with the formulation of clinical guidelines for the management of these neoplasms. In this session we will outline age-related issues that deserve special attention and possible approaches.

2.3.5a. Acute Myelogenous Leukemia. The incidence of Acute Myelogenous Leukemia increases with age. The prognosis of AML in older individuals is poorer than in younger individuals for a number of reasons including higher prevalence of multidrug resistance, unfavorable cytogenetic changes and hypoplastic marrow [130]. In addition, poor patient conditions may make these individuals more vulnerable to treatment complications. Common sense dictates that if AML in a person aged 60 and over is treated with standard chemotherapy, this should be done preferentially in a cancer center, where supportive care with blood product and antibiotics is easily available and where a dedicated staff may provide all attention these patients need and deserve. In addition to reversal of MDR, issues to be defined include less toxic forms of induction, including monoclonal antibodies and new

medications, value of supportive treatment with growth factor in patients with hypoplastic disease or myelodysplasia.

2.3.5b. Non-Hodgkin's Lymphomas.

The incidence of these conditions increases with age, and age of 60 and higher is generally considered a poor prognostic factor [131]. For large cell lymphoma there is general agreement that maintenance of the dose intensity of chemotherapy should be maintained and that filgrastim or pegfilgrastim be used to minimize myelosuppression and allow administration of chemotherapy in time. There is also general agreement the combination of rituximab and chemotherapy with CHOP is superior to CHOP alone [90]. Issues to be defined include the value of dose dense chemotherapy [101], the management of individuals with cardiovascular diseases preventing the use of an anthracycline, and the value of weekly chemotherapy over a shorter period of time [89].

For low grade lymphoma the main issue is when treatment should be initiated, and what is the most effective initial treatment, whether low dose single agent chemotherapy, combination chemotherapy, monoclonal antibodies or a combination of these compounds. Also the role of radioimmunochemotherapy should be defined.

2.3.5c. Breast Cancer. The main area of controversy is the use of adjuvant chemotherapy in women over 70, and in particular the balance of benefits and risks: A number of decision analyses may assist the practitioner in this decision [132, 133]. It appears reasonable to recommend that the use of chemotherapy be guided by an individual estimate of risk and benefit rather than by the patient chronologic age. Other issues include long-term complications of adjuvant aromatase inhibitors, and the use of single agent or combination chemotherapy in metastatic disease.

2.3.5d. Non-Small Cell Lung Cancer. The incidence of this disease among older individuals is progressively increasing [133]. The issues of concern include benefits and risk of simultaneous versus sequential radiation and chemotherapy in older individuals with locally advanced disease [134], the benefits of combination vs single agent chemotherapy in metastatic disease, and the need of a platinum compound in older individuals [135-137].

2.3.5e. Cancer of the Large Bowel. A recent meta-analysis clearly showed similar benefits of adjuvant chemotherapy for stage III disease in patients below 50 and in those over 70 [138]. Issue of interest concern the use of oral preparation and especially capecitabine in lieu of fluorinated pyrimidines and

the benefits of combination chemotherapy both in the adjuvant and the metastatic setting.

3. CONCLUSIONS

The review allows the following conclusions:

1. Some form of geriatric assessment appear beneficial for older cancer patients; this assessment may allow to estimate life-expectancy and tolerance of treatment, to reveal reversible conditions that may influence the treatment, and to provide a common language to classify older individuals in clinical practice and clinical trials. The geriatric assessment is also the background of any decision analysis related to the study and the management of older patients, capable to accommodate new insights in the biology of cancer and aging and to address problems related to the management of specific diseases.
2. Some age related changes may affect the pharmacology of antineoplastic agents in the majority of older individuals and justify some general guidelines for the administration of chemotherapy that include:
    - Adjustment of the doses of the first chemotherapy to the glomerular filtration rate in individuals aged 65 and older. If no toxicity is observed, the following doses should be increased to prevent under-treatment
    - Prophylactic use of filgrastim or pegfilgrastim in patients aged 65 and older receiving chemotherapy of moderate dose intensity, comparable to CHOP
    - Maintenance of the hemoglobin of patients receiving chemotherapy at 12 gm/dl or higher
    - Aggressive management of mucositis with timely fluid resuscitation
    - Prevention of mucositis by substituting capecitabine for intravenous fluorinated pyrimidine

Specific guidelines for the management of individual diseases may be necessary as illustrated. The geriatric assessment may provide the framework of reference to estimate benefits and risks.

REFERENCES

1. Balducci L; Beghe' C: The application of geriatric principles to the management of the older cancer patient. Crit Rev Oncol Hematol, 2000, 35, 147-154
2. Cova D; Balducci L: Cancer chemotherapy in the older person. In Balducci L; Lyman GH; Ershler WB: Comprehensive Geriatric Oncology 2003, in press
3. Balducci L, Yates G: General guidelines for the management of older patients with cancer. Oncology, NCCN Proceedings, November 2000, 221-7
4. Repetto L; Biganzoli L; Kohene CH et al: EORTC cancer in the elderly task force guidelines for the use of colony-stimulating factors in elderly patients with cancer. Eur J Canc, 2003, 39, 2264-2272
5. Ozer H; Artmitage JO; Bennett CL; Crawford J; Demetri GD et al: 2004 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol, 2004, in press
6. Siddall R: Managers and medicine: weight of evidence. Health Service J, 2002, 112, 34-36
7. Harris RP; Helfan M; Woolf SH et al: Current methods of the US Preventive Service Task Force: a review of the process. Am J Prev Med, 2001, 20 (3 suppl), 21-35
8. Balducci L: The geriatric cancer patient: equal benefit from equal treatment. Cancer Control: Journal of the Moffitt Cancer Center, March/April, 8:Suppl 2:1-25, 2001
9. Reuben DB; Rubenstein LV; Hirsch SH et al: Value of functional status as predictor of mortality. Am J Med, 1992, 93, 663-669
10.Inouye SK; Peduzzi PN; Robison JT et al: Importance of functional measures in predicting mortality among older hospitalized patients. JAMA, 1998, 1187-1193
11.Siu AL; Moshita L; Blaustein J: Comprehensive geriatric assessment in a day hospital. J Am Ger Soc, 1994, 42, 1094-1099
12.Ramos LR; Simoes EJ; Albert MS: Dependence in activities of daily living and cognitive impairment strongly predicted mortality in older urban residents in Brazil. J Am Ger Soc, 2001,49, 1168-1175
13.Walter LC; Brand RJ; Counsell RS et al: Development and validation of a prognostic index for 1 year mortality in older adults after hospitalization JAMA 2001, 285,2987-2993
14. Stump TE; Callahan CM; Hendrie HC: Cognitive impairment and mortality in Older Primary care patients. J Am Ger Soc, 2001, 49, 934-940
15.Nakanishi N; Tatara K; Ikeda K et al: Relation between intellectual dysfunction and mortality in community-residing older people. J Amer Ger Soc, 1998, 46, 583-589
16.Eagles JM; Beattie JAG; Restall DB et al: Relationship between cognitive impairment and early death in the elderly. Br Med J, 1990, 300, 239-240
17.Bruce ML; Hoff RA; Jacobs SC et al: The effect of cognitive impairment on 9-year mortality in a community sample. J Gerontol, 1995, 50B;P289- 296
18.Kivela S-L; Pahkala K: Depressive disorder as predictor of physical disability in old age. J Am Geriatr Soc, 2001, 290-296
19.Blazer DG; Hybels CF; Pieper CF: The association of depression and mortality in elderly persons: a case for multiple independent pathways. J Gerontol Med Sci, 2001, 56A, M505-509
20.Covinsky KE; Kahana E; Chin MH et al: De ressive Symptoms and three-year mortality in older hospitalized medical patients. Ann Int Med, 1999, 130, 563-569
21.Bruce ML; Leaf PJ; Rozal GP et al: Psychiatric Status and nine year mortalitydata in the new haven Epidemiologic catchment Area Study. Am J Psych, 1994, 151, 716-721
22.Lyness JM; Ling DA; Cox C et al: The importance of subsyndromal depression in older primary care patients. Prevalence and associated functional disability. J Am Ger Soc, 1999, 47, 647-652
23.Lyness JM; Noel TK; Cox C et al: Screening for depression in elderly primary care patients: a comparison of the center for Epidemiologic Studies Depression Scale and the Geriatric Depression Scale. Arch Intern Med, 1997, 157, 449-454

24.Satariano WA & Ragland DR: The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Int Med, 1994, 120, 104-110
25.Piccirillo JF; Feinstein AR: Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer, 1996, 77, 834-842
26.Yancik R; Ganz PA; Varricchio CG et al: Perspectives on comorbidity and cancer in the older patient: approach to expand the knowledge base. J Clin Oncol, 2001,19,1147-1151
27.Tinetti ME; Williams CS: The effects of falls and fall injuries in functioning in community dwelling older persons. J Gerontol, 1998, 53A M112-119
28.Rockwood K; Stadnyk K; Macknigt C et al: A brief instrument to classify frailty in elderly people. Lancet, 1999,353, 205-206
29.Bucht G; Gustafson Y; Sandberg O: Epidemiology of delirium. Dement Ger Cogn Disord, 1999, 10, 315-318
30.Verdery RB: Failure to thrive in old age: follow-up on a workshop. J Gerontol Biol Scie Med.l997, 52, M333-336
31.Pavlik VN; Hyman DJ; Festa NA: Quantifying the problem of abuse and neglect in adults: analysis of a statewide database. J Am Ger Soc, 2001, 49, 45-48
32.Lachs MS; Williams C; O'Brien S et al: Risk factors for reported elder abuse and neglect: a nine-year observational cohort study. Gerontologist, 1997, 37, 469-474
33.Dyer CB; Pavlick VN; Murphy KP et al: The high prevalence of depression and dementia in elder abuse or neglect. J Am Ger Soc, 2000, 48, 205-208.
34.Njegovan V; Hing MM; Mitch SL et al: The hierarchy of functional loss associated with cognitive decline I older persons. J Gerontol A Biol Sci Med Sci, 2001, 56, M638-643
35.Walter LC; Covinsky KE: Cancer screening in elderly patients: a framework for individual decision making. JAMA, 2001, 285, 2750-2756
36.Extermann M; Chen A; Cantor AB et al: Predictors of toxicity from chemotherapy in older patients. Proc Am Soc Clin Oncol, 2000, 19, 617a
37.Zagonel V; Fratino L; Piselli P et al: The comprehensive Geriatric Assessment predicts mortqality among elderly cancer patients. Proc Am Soc Clin Oncol, 2002,, 21, 365 a, abstr 1458
38.Extermann M; Overcash J; Lyman GH et al: Comorbidity and functional status are independent in older cancer patients. J Clin Oncol, 1998, 16,1582-1587
39.Repetto L; Fratino L; Audisio RA et al: Comprehensive geriatric assessment adds information to the Eastern Cooperative Group Performance status in elderly cancer patients. An Italian Group for Geriatric Oncology Study. J Clin Oncol, 2002, 20, 494-502
40.Ingram SS; Seo PH; Martell RE et al: Comprehensive assessment of the elderly cancer patient: the feasibility of self-report methodology. J Clin Oncol, 2002, 20, 770-775
41.Extermann M; Chen H; Cantor AB; Corcoran MB; Meyer J; Grendys E; Cavanaugh D; Antonek S; Camarata A; Haley WE; Balducci L: Predictors of tolerance to chemotherapy in older cancer patients: a prospective pilot study. European Journal of Cancer, 38, 1466-1473, 2002
42.Cohen HJ; Feussner JR; Weinberger M et al: A controlled trial of inpatient and outpatient geriatric assessment. N Engl J Med, 2002, 346,905-912
43.Reuben DB; Franck J; Hirsch S et al: A randomized clinical trial of outpatient geriatric assessment (CGA), coupled with an intervention, to increase adherence to recommendations. J Am Ger Soc, 1999, 47, 269-276.
44.Bula CJ; Berod AC; Stuck AE et al: Effectiveness of preventive in-home geriatric assessment in well functioning, community dwelling older people: secondary analysis of a randomized trial. J Am Ger Soc, 1999, 47, 389-395
45.Tulloch AJ; Moore V: A randomized controlled trial of geriatric screening and surveillance in general practice. J R Coll Gen Pract, 1979, 29, 733-742
46.Landi F; Onder G; Russo A et al: A new model for integrated home care in the elderly: impact on hospital use. J Clin Epidemiol, 2001, 54, 968-970

47.Bernabei R; Venturiero V; Tarsitani P et al: The comprehensive geriatric assessment: when, where, how. Crit Rev Hematol Oncol, 2000, 33,45-56
48.Boult C; Boult LB; Morishit L et al: A randomized clinical trial of outpatient geriatric evaluation and management. J Am Ger Soc, 2001, 49, 351-359
49.Inouye SK; Bogardus ST; Charpentier PA et al: A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med, 1999, 340:669-674
50.Tinetti ME; McAvay G; Claus G et al: A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med, 1994, 331, 821-827
51.McCorkle R; Strumpf NE; Nuamah IF et al: A specialized home care intervention improves survival among old post-surgical cancer patients. J Am Ger Soc, 2000, 48, 1707-1713
52.Burns R; Nichols LO; Martindale-Adams J et al: Interdisciplinary geriatric primary care evaluation and management. Two-year outcomes. J Am Ger Soc, 2000, 48, 8-13
53.Stuck AE; Siu AL; Wieland GD et al: Comprehensive geriatric assessment: meta-analysis of controlled trials. Lancet, 1993, 342, 1032-1036
54.Stuck AE; Egger M; Beck JC et al: A controlled trial of geriatric evaluation. N Engl J Med, 2002,347, 371-373
55.Hamerman D: Toward an understanding of frailty. Ann Intern Med, 1999, 130, 945-950
56.Balducci L and Stanta G: Cancer in the frail patient: a coming epidemic. Hematol Oncol Clin N America, 2000, 14, 235-250
57.Fried LP; Tangen CM; Walston J et al: Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci, 2001, 56A, M146-M156
58.Saliba D; Elliott M; Rubenstein LZ et al: The vulnerable elders survey: a tool for identifying vulnerable older people in the community. J Am Ger Soc, 2001,49, 1691-1699
59.Ferrucci L; Harris TB; Guralnik JM et al: Serum Il-6 level and the development of disability in older persons. J Am Ger Soc, 1999, 47, 639-646
60.Cohen HJ; Pieper CF; Harris T: Markers of inflammation and coagulation predict decline in function and mortality in community-dwelling elderly. J Am Ger Soc, 2001, 49, S1, A3
61.Martin F: Frailty and somatopause. Growth Hormone IGF Res, 1999, 9, 3
62.Binder EF; Schechtman KB; Ehsani AA et al: Effects of exercise training on frailty in community dwelling older adults: results of a randomized controlled trial. J Am Ger Soc, 2002, 50, 1921-1928
63.Hamerman D; Berman JV; Albers GW et al: Emerging evidence of inflammation in conditions frequently affecting older adults: reports of a symposium. J Am Ger Soc, 1999, 47, 1016-1025
64.Extermann M; Bonetti M; Sledge GW; O'Dwyer PJ; Bonomi P; Benson AB III: MAX2: A convenient index to estimate the average per patient risk of chemotherapy toxicity (in submission)
65.Lachs MS; Feinstein AR; Cooney LM et al: A simple procedure for general screening for functional disability in elderly patients. Ann Intern Med, 1990, 112, 699-706
66.McDermott M; Greenland P; Ferrrucci L et al: Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. J Am Ger Soc, 2002, 50, 247-255
67.Pavol MJ; Owings TM; Foley KT et al: Influence opf lower extremities strength of healthy older adults on the outcome of induced trip. J Am Ger Soc, 2001, 50, 256-262
68.Daltroy LH; Larson MG; Eaton HM et al: Discrepancies between self-reported and observed physical function in the elderly: the influence of response shift and other factors. Soc Sci Med, 1999, 48, 1549-1561
69.Merrill SS; Seeman TE; Kasl SV et al: Gender differences in the comparison of self-reported disability performance measures. J Gerontol Biol Sci Med Sci, 1997, 52, 19-26
70.Gill TM; Baker D; Gottshalk M et al: A program to prevent functional decline in physically frail, elderly persons who live at home. N Engl Jrnl Med, 2002, 347, 1068-1074

71. Terret C: Management and geriatric assessment of cancer in the elderly. Expert Rev Anticancer Ther, 2004, 4, 669-675
72.Ershler WB; Keller ETR: Age-associated increased interleukin-6 gene expression, late life disease and frailty. Ann Rev Med, 2000, 51, 245-270
73.Wilson CJ; Cohen HJ; Pieper CF: Cross-linked fibrin degradation products (D-dimer) , plasma cytokines, and cognitive decline in community dwelling elderly persons. J Am Ger Soc, 2003, 51, 1374-1381
74.Duthie E: in Balducci L; Lyman GH; Ershler WB: Comprehensive Geriatric Oncology, 2003, in press
75.Gelman RS; Taylor SG: Cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy in women more than 65-year-old with advanced breast cancer. The elimination of age trends in toxicity by using doses based on creatinine clearance. J Clin Oncol, 1984, 2, 1406-1414
76.Gurney H: Dose calculations of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin One, 1996, Vol. 14:2590-2611
77.Waller DG; Fleming JS; Ramsay B et al: The accuracy of creatinine clearance with and without urine collection as a measure of glomerular filtration rate. Postgrad Med J, 1991, 67, 42-46
78.Levey AS; Bosch JP; Lewis JB et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med, 1999, 130, 461-470
79.Kintzel PE; Dorr RT: Anticancer Drug Renal Toxicity and elimination: dosing guidelines for altered renal function. Cancer Treat Rev, 1995,21,33-64
80.Kim YJ; Rubenstein EB; Rolston KV et al: Colony-stimulating factors (CSFs) may reduce complications and death in solid tumor patients with fever and neutropenia. Proc ASCO, 2000, 19, 612a, abstr 2411
81.Begg CB; Carbone P: Clinical trials and drug toxicity in the elderly. The experience of the Eastern Cooperative Oncology Group. Cancer, 1983, 52, 1986-1992
82.Crivellari D; Bonetti M; Castiglione-Gertseh M et al: Burdens and benefits of adjuvant cyclophosphamide, methotrexate and fluorouracil and Tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial vii. J Clin Oncol, 2000, 18, 7, 1412-1422
83.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
84.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 13:2530-2539, 1995
85.Tirelli U; Errante D; Van Glabbeke M et al: CHOP is the standard regimen in patients $\geq$ 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, 1998,16,27-34
86.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 Groupe d'Etude des Lymphomes de l'Adulte Study on 453 patients older than 69 years. J Clin Oncol 15: 2945-2953, 1997
87.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 subgroups with differing hematologic toxicity. J Clin Oncol 16:2352-2358,1998
88.Osby E; Hagberg H; Kvaloy S et al: CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. Blood, 2003, 101, 3840-3848

89.O'Reilly SE; Connors JM; Howdle S et al: In search of an optimal regimen for elderly patients with advanced-stage diffuse large-cell lymphoma: results of a phase II study of P/DOCE chemotherapy. J Clin Oncol 2250-2257, 1993

90.Coeffier B; Lepage E; Briere J; Herbrecht R; Tilly H; Bouabdallah R; Morel P; Van Den Neste, E; Salles G; Gaulard P; Reyes F; Lederlin P; Gisselbrecht C: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med, Jan 24; 346(4): 235-42, 2002

91.Doorduijn JK; van derr Holt B; van der Hem KG et al: Randomized trials of granulocyte-colony stimulating factor (G-CSF) added to CHOP in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol, 2003, 21, 2041-2050

92.Morrison VA; Picozzi V; Scotti S et al: The impact of age on delivered dose-intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-Hodgkin's lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. Clin Lymphoma, 2001, 2, 47-56

93.Dees EC, O'Reilly S, Goodman SN, Sartorius S, Levin MA, Jones RJ, Donehower RC; Fetting JH: A prospective pharmacologic evaluation of age-related toxicity and adjuvant chemotherapy in women with breast cancer. Cancer Invest, 2000, 18(6): 521-9

94.Bertini M; Freilone R; Vitolo U et al: The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: Feasiblity and efficacy of an intensive multidrug regimen. Leukemia Lymphoma 22:483-493, 1996

95.Price TH; Chatta GS; Dale DC: Effect of recombinant granulocyte colony-stimulating factor on neutrophil kinetics in normal young and elderly humans. Blood, 1996, 88,335-340

96.Zagonel V; Babare R; Merola MC et al: Cost-benefit of granulocyte colony-stimulating factor administration in older patients with non-Hodgkin's lymphoma treated with combination chemotherapy. Ann Oncol, 1994, 5, suppl 2 127-132

97.Lyman GH; Kuderer N: In: Balducci L; Lyman GH; Ershler WB: Comprehensive Geriatric Oncology, 2003, in press

98.Chrischilles E; Delgado DI; Stolshek BS et al: Impact of age and colony stimulating factor use in hospital length of stay for febrile neutropenia in CHOP treated non-Hodgkin's lymphoma patients. Cancer Control, 2002, 9, 203-211

99.Meyer RM; Browman GP; Samosh ML et al: Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. J Clin Oncol, 1995, 13, 2386-2393

100.Dixon DO, Neilan B, Jones SE, Lipschitz DA, Miller TP, Grozea PN, Wilson HE: Effect of age on therapuetic outcome in advanced diffuse hisiocytic lymphoma: the Southwest Oncology Group experience. Clin Oncol, 1986, Vol. 4, 295-305

10l.Wunderlich A; Kloess M; Reiser M et al: Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High Grade Non-Hodgkin's Lymphoma Study Group. Ann Oncol, 2003, 14, 881-893

102.Kerr KG: The prophylaxis of bacterial infections in neutropenic patients. J. Antimicrob Chemother, 1999 Nov; 44(5): 587-91

103.Rowe JM; Andersen JW; Mazza JJ et al: Randomized placebo-controlled phase III study of granulocyte-macrophage colony stimulating factor in adult patients > 55-70 years with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood, 1995, 86, 457-462

104.Witz F; Sadoun A; Perrin MC: A placebo-controlled study of recombinant human granulocyte macrophage colony-stimulating factor administered during an induction treatment for "de novo" acute myelogenous leukemia in older patients. Blood, 1998, 15, 2722-2730

105.Dombret H; Chastang C; Fenaux P et al: A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. N Engl J Med, 1995, 332, 1678-1683

106.Balducci L; Hardy CL; Lyman GH: Hemopoietic growth factors and age. Curr Opinion Hematol, 2001, Vol. 8, No. 3, 170-87
107.Hartman LC; Tschetter LK; Haberman TM et al: Granulocyte colony-stimulating factor in severe chemotherapy induced febrile neutropenia. N Engl J Med, 1997,336, 1776-1780
108.Kouroukis CT; Browman GP; Esmail R et al: Chemotherapy for older patients with newly diagnosed, advanced stage, aggressive histology non-Hodgkin lymphoma: a systematic review. Ann Intern Med, 2002, 136, 144-152
109.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
110.Ratain MJ; Schilsky RL; Choi KE et al: Adaptive control of etoposide administration: impact of interpatient pharmacodynamic variability. Clin Pharmacol Ther, 1989, 45, 226-233
111.Silber JH; Friedman M; Di Paola RS et al: First-cycle blood counts and subsequent neutropenia, dose reduction or delay in early stage breast cancer therapy. J Clin Oncol, 1998, 16, 2392-2400
112.Schijvers D; Highley M; DeBruyn E et al. Role of red blood cell in pharmakinetics of chemotherapeutic agents. Anticancer Drugs, 1999, 10, 147-53
113.Klein CE; Gupta E; Reid JM et al: Population pharmacokinetic model for irinotecan and two of its metabolites: SN-38 and SN-38 glucuronide. Clin Pharmacol Ther, 2002,72,638-647
114.Balducci L; Hardy CH: Anemia in the older cancer patient. In: Balducci L; Lyman GH; Ershler WB: Comprehensive Geriatric Oncology, 2003, in press
115.Chaves PH; Volpato S; Fried L: Challenging the world health organization criteria for anemia in the older woman. J Am Ger Soc, 2001, 49, S3, A10
116.Nissenson AR; Goodnough LT; Dubois RW et al: Anemia: not just an innocent bystander. Arch Intern Med, 2003,163, 1400-1404
117.Ferrucci JAGS, in press
118.Kikuchi M; Inagaki T; Shinagawa N: Five-year survival of older people with anemia: variation with hemoglobin concentration. J Am Ger Soc, 2001, 49, 1226-1228
119.Izaks GJ; Westendorp RGJ; Knook DL. The definition of anemia in older persons. JAMA. 1999; 281(18): 1714–7
120.Anía BJ, Suman VJ, Fairbanks VF, et al. Incidence of anemia in older people: an epidemiologic study in a well defined population. J Am Geriatr Soc, 1997, Jul: 45(7):825-31
121.Lee WR; Berkey B; Marcial V et al: Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck cancer: a secondary analysis of RTOG 85-27. Int J Rad Oncol Biol Phys, 1998,42, 1069-1075
122.Dunst J; Kuhnt T; Strauss HG et al: Anemia in cervical cancer: impact on survival, patterns of relapse, and association with hypoxia and angiogenesis. Int J Rad Oncol Biol Phys, 2003, 56,778-787
123.Gabrilove JL; Einhorn LH; Livingston RB et al: Once-weekly dosing of epoetin alfa is similar to three-times weekly dosing in increasing hemoglobin and quality of life. Proc Am Soc Clin Oncol 1999; 18:574a
124.Cleeland CS; Demetri GD; Glaspy J et al: Identifying hemoglobin levels for optimal quality of life. Results of an incremental analysis. Proc Am Soc Clin Oncol 1999; 18:574A (abstract 2215)
125.Liao S; Ferrell BA: fatigue in an older population. J Am Ger Soc, 2000, 48, 426-430Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant 2000; 15(3): 14–8
126.Metivier F; Marchais SJ; Guerin A; Pannier B, London GM: Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant, 2000:15(3): 14-8
127.WU WC; Rathore SS; Wang Y et al: Blood transfusions in elderly patients with acute myocardial infarction, N Engl Jrnl Med, 2001, 345, 1230-1236

128.Pickett JL; Theberge DC; Brown WS; Schweitzer SU; Nissenson AR:. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999; 33(6): 1122–30

129.Carreca I; Balducci L: Oral chemotherapy in the older cancer patient. Am J Cancer, 2002, in press

130.Buchner T: Acute leukemia in the elderly. In: Balducci L; Lyman GH; Ershler WB: Comprehensive Geriatric Oncology, 2003, in press

131.The International Non-Hodgkin's Lymphoma Prognostic Factors Project: a predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med, 1993,329,987-994

132.Extermann M; Balducci L; Lyman G: What threshold for adjuvant tamoxifen in older breast cancer patients? A decision analysis. Eur Jrnl Can 34(suppl 1):S40, 1998

133.Baum M; Ravdin PM: Decision making in early breast cancer: guidelines and decision tools. Eur J Cancer, 2002, April; 38(6):745-9

134.Balducci L; Beghe C: Prevention of cancer in the older person. Clinics in Geriatric Medicine, 18, 505-28, 2002

135.Langer C; Scott C; Byhardt R et al: Effect of advanced age on outcome of Radiation Therapy Oncology Group Studies of locally advanced NSCLC. Lung Cancer 2000, 29, (suppl 1), 104

136.Gridelli C; Perrone F; Gallo C et al: Chemotherapy for elderly patients with advanced non-small-cell lung cancer in the elderly study (MILES) phase III randomized trial. J Natl Cancer Inst, 2003, 95, 341-343

137.Frasci G; Lorusso V; Panza N et al: Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non small cell lung cancer. J Clin Oncol, 2000, 18, 2529-2536

138.Sargent DJ; Goldberg RM; Jacobson SD et al: A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med, 2001, 345, 1091-1097