# Supplement Files

Do age, fitness and concomitant medications influence management and outcomes of chronic lymphocytic leukemia patients treated with ibrutinib?

Alessandra Tedeschi,[1] Anna Maria Frustaci,[1] Francesca Romana Mauro,[2] Annalisa Chiarenza,[3] Marta Coscia,[4] Stefania Ciolli,[5] Gianluigi Reda,[6] Luca Laurenti,[7] Marzia Varettoni,[8] Roberta Murru,[9] Claudia Baratè,[10] Paolo Sportoletti,[11] Antonino Greco,[12] Chiara Borella,[13] Valentina Rossi,[14] Marina Deodato,[1] Annalisa Biagi,[15] Giulia Zamprogna,[1] Angelo Curto Pelle,[3] Gianfranco Lapietra,[2] Candida Vitale,[4] Francesca Morelli,[5] Ramona Cassin,[6] Alberto Fresa,[7] Chiara Cavalloni,[8] Massimiliano Postorino, [15]Claudia Lelo,[2] Roberto Cairoli,[1] Francesco Di Raimondo,[3] Marco Montillo,[1] Giovanni Del Poeta[15]

1 Department of Hematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

2 Hematology, Department of Translational and Precision Medicine, Sapienza University, Policlinico Umberto I, Roma, Italy

3 Division of Hematology, A.O.U. "Policlinico-Vittorio Emanuele", University of Catania, Italy

4 Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino and Department of Molecular Biotechnology and Health Sciences, University of Torino, Italy

5 Department of Hematology, Università degli Studi di Firenze, Italy

6 Department of Hematology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

7 Hematology Institute, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Roma,Italy

8 Division of Hematology Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

9 Hematology and Stem Cell Transplantation Unit, Ospedale A. Businco, ARNAS “G. Brotzu”, Cagliari, Italy

10 Department of Clinical and Experimental Medicine, Section of Hematology, University of Pisa, Italy

11 Department of Medicine, Division of Hematology and Clinical Immunology, University of Perugia, Italy

12 Department of Hematology, Azienda Ospedaliera Giovanni Panìco, Tricase, Italy

13 Department of Hematology, Ospedale San Gerardo, Monza, Italy

14 Hematology & Transfusion Medicine L. Sacco University Hospital & School of Medicine, Milano, Italy

15 Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Roma, Italy

**Supplement Appendix 1. List of CYP3A inhibitors**

| **Strong CYP3A Inhibitors** |
|---|
| **Antibiotics:** clarithromycin, telithromycin, troleandomycin |
| **Antifungals:** itraconazole, ketoconazole, posaconazole, voriconazole |
| **Antivirals:** boceprevir, telaprevir |
| **Other:** cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone |
| **Protease inhibitors:** indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir |
| **Moderate CYP3A Inhibitors** |
| **CYP3A4, CYP3A5, CYP3A7** |
| **Antibiotics:** ciprofloxacin, erythromycin |
| **Antifungals**: fluconazole, clotrimazole |
| **Protease inhibitors:** amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir |
| **Calcium channel blockers:** diltiazem, verapamil |
| **Tyrosine kinase inhibitors (anticancer):** imatinib, crizotinib |
| **Food products:** grapefruit juice (citrus paradisi juice) |
| **Herbal medications:** Schisandra sphenanthera |
| **Others:** amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam, cimetidine |
| **Strong CYP3A Inhibitors** |
| **Antibiotics:** clarithromycin, telithromycin, troleandomycin |

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.

1. Source: Imbruvica (Ibrutinib) US Food and Drug Adminitration Highlights of prescribing information https.//www.accessdata.fda.gov>label) accessed 18 May 2021

**Supplement Appendix 2. Weighted index of comorbidity***

| Assigned weights for disease | Conditions |
|---|---|
| 1 | Myocardial infarct |
| | Congestive heart failure |
| | Peripheral vascular disease |
| | Cerebrovascular disease |
| | Dementia |
| | Chronic pulmunary disease |
| | Connective tissue disease |
| | Ulcer disease |
| | Mild liver disease |
| | Diabetes |
| 2 | Hemiplegia |
| 3 | Moderate or severe renal disease |
| | Diabetes with end organ damage |
| | Any tumor |
| | Leukemia |
| | Lymphoma |
| | Moderate or severe liver disease |
| 6 | Metastatic solid tumor |
| | AIDS |

Assigned weigths for each condition that a patient has. The total equals the score

* Medical conditions that were deemed to be complications of CLL (eg, anemia, thrombocytopenia, and splenomegaly) were not included as part of the total CIRS score

1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

**Supplement Appendix 3. The Modified Cumulative Illness Rating Scale (CIRS)***

| Body system | Score | | | | |
|---|---|---|---|---|---|
| 1. Cardiac (heart only) | 0 | 1 | 2 | 3 | 4 |
| 2. Hypertension (rating is based on severity; organ damage is rated separately) | 0 | 1 | 2 | 3 | 4 |
| 3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics) | 0 | 1 | 2 | 3 | 4 |
| 4. Respiratory (lungs, bronchi, trachea below the larynx) | 0 | 1 | 2 | 3 | 4 |
| 5. EENT (eye, ear, nose, throat, larynx) | 0 | 1 | 2 | 3 | 4 |
| 6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes) | 0 | 1 | 2 | 3 | 4 |
| 7. Lower GI (intestines, hernias) | 0 | 1 | 2 | 3 | 4 |
| 8. Hepatic (liver and biliary tree) | 0 | 1 | 2 | 3 | 4 |
| 9. Renal (kidneys only) | 0 | 1 | 2 | 3 | 4 |
| 10. Other GU (ureters, bladder, urethra, prostate, genitals) | 0 | 1 | 2 | 3 | 4 |
| 11. Muscolo-skeletal-integumentary (muscle, bone, skin) | 0 | 1 | 2 | 3 | 4 |
| 12. Neurological (brain, spinal cord, nerves, do not include dementia) | 0 | 1 | 2 | 3 | 4 |
| 13. Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity) | 0 | 1 | 2 | 3 | 4 |
| 14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis) | 0 | 1 | 2 | 3 | 4 |

* Medical conditions that were deemed to be complications of CLL (eg, anemia, thrombocytopenia, and splenomegaly) were not included as part of the total CIRS score

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the Cardiac system (e.g. rating is 4).

The spread of a cancer may lead to rate the condition in more than one category. For example, a lung cancer with bone metastases treated with nonsteroidal anti-inflammatory drugs (NSAID) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

0 - No problem affecting that system or past problem without clinical relevance.

1 - Current mild problem or past significant problem.

2 - Moderate disability or morbidity and/or requires first line therapy.

3 - Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).

4 - Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN bronchodilators, occasional heartburn relieved with PRN antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).

Level 2: No evidence of recurrence or sequel in the past 5 years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the “judgement strategy” that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

HEART

In this category only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocardities, miocardities, pericardities, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, PMK placement), heart malignancies. Functional impact must be considered too, e.g. NYHA II heart failure has different value between dependent and independent persons.

0. No problems

1. Remote MI (>5 years ago); occasional [exertion] angina; asymptomatic valvular disease

2. CHF compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter EKG monitoring); valvular disease requiring medical treatment

3. Previous MI (<5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis

4. Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0. Normotension

1. Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)

2. Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)

3. Hypertension requiring two or more pills for control

4. Malignant hypertension, or hypertension non controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);

Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;

Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy;

Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease;

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0. No problem

1. Venous insufficiency, varices, lymphedema; carotid stenosis <70%; hemoglobin 10-12 g/dl (in females), 12-14 g/dl (in males); anemia of chronic “inflammatory” disease

2. Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g. anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis >70%; aortic aneurysm <4 cm; hemoglobin 8-10 g/dl (in females), 10-12 g/dl (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000-4000/mmc; mild thrombocytopenia (50000-150000/mmc)

3. DVT or recent DVT (<6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin <8g/dl (in females), <10 g/dl (in males); dyserythropoietic anemia; WBC <2000/mmc; severe thrombocytopenia (<50000/mmc)

4. Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g. aortic aneurysm >4 cm, symptomatic carotid stenosis >70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category we consider COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status too.

0. No problem

1. Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker >10 but <20 pack years

2. Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, TC, spirometry); daily prn inhalers (≤2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker <20 but <40 pack years

3. exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient

4. Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to lifetime pack years:

Number of cigarette packs smoked per day X Number of years smoked in their lifetime

e.g. 1 pack year = 20 cigarettes/die (1 pack) X 1 year

Ex-smokers should be rated too, but those who have been smoke free for the most recent 20 years would merit a lower rating than currently smoking

Examples:

A. Patient smoking 20 cig/die (1 pack) for 25 years = 25 pack years - CIRS score: 2

B. Patient smoking 40 cig/die (2 packs) for 25 years = 50 pack years – CIRS score: 3

C. Ex-smoker of 20 cig/die (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

D. Ex smoker of 20 cig/die (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated after instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

0. No problems

1. Corrected vision with glasses; mild hearing loss; chronic sinusitis

2. Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds

3. Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)

4. Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if “organically” he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

## UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, GERD, hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. Pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Pay attention that type 1 diabetes is rated under “metabolic”.

0. No problem

1. Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (>5 years ago); previous H. Pylori eradication therapy (>5 years ago)

2. Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or H.P. eradication therapy within 5 years

3. Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis

4. Any type of malignancies (see “Rating Malignancies”); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

## LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the G.I. system, from small bowel to anus: Whipple’s disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0. No problems, previous appendectomy, previous hernia repair (without complications)

1. Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)

2. Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (>5 years ago)

3. Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bysacodil, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (<5 years ago)

4. Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0. No problem

1. History of hepatitis (actually normal values of transaminases); cholecystectomy

2. Cholelithiasis; chronic hepatitis or previous hepatitis (<5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in “psychiatric”, too)

3. Chronic hepatitis or any other liver disease with marked elevation of transaminases (>3-times normal values); elevated bilirubin

4. Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.

Bence-Jones proteinuria in multiple myeloma should not be considered.

0. No problem

1. Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria

2. Serum creatinine >1.5 but <3 mg/dl without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds

3. Serum creatinine >3 mg/dl or >1.5 mg/dl in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient

4. Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra.

Genitals, prostate, testicles, penis, seminal vesicles.

Uterus, ovaries. Mammary gland is rated under “metabolic”.

This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTI’s), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0. No problem

1. Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)

2. Pathological pap smear (or 2 consecutives abnormal); frequent UTI’s (3 or more in the past year) in female or current UTI’s; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi

3. Prostatic cancer in situ (e.g. incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps

4. Acute urinary retention; current urosepsis; any GU malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very wide category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

NOTICE: score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0. No problem

1. Requires PRN meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year

2. Daily anti-osteoarthritis meds (NSAID) or use of assisitive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability

3. Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures

4. Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscular diseases.

## CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the “somatic” pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson’s disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0. No problem (or fewer convulsions in childhood)

1. Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.

2. Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.

3. Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.

4. Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer’s disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer’s disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g. Parkinson’s Disease), both “neurologic” and “psychiatric” categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings too)

Type 1 and type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors didn't find a more appropriate one; so it includes the breast cancer too.

Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0. No problem

1. Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m2); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.

2. Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c <7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m2); hyperthyroidism (Basedow, Plummer) in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.

3. Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL>100 mg/dl in patients with previous myocardial infarction or stroke); severe obesity (BMI >45 kg/m2); symptomatic hyperparathyroidism (for instance, hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.

4. Uncontrolled diabetes (hemoglobin A1c >8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c >7%, total cholesterol >250 mg/dl), score the pathology according to the laboratory values, which really define its severity.

## PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale, Neuro-Psychiatric Inventory if available) (8, 9).

0. No psychiatric problem or history thereof

1. Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g. BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).

2. A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).

3. Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.

4. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE <15); delirium (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.


1. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, Spazzafumo L, Mancinelli L, Espinosa E, Rappelli A, Dessì-Fulgheri P. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc.* 2008; 56(10):1926-1931.


**Supplement Table 1. Detailes on patients permanentely reducing or definitively discontinuing ibrutinib due to cardiologic adverse events.**

| Pt | Age | ECOG-PS | CIRS | CCI | Previous cardiocomorbidity | Antiplatelets/ Anticoagulant* | Cardiovascular concomitant medications * | Cardiac AE During Ibrutinib tx | Action on ibrutinib (Months from Ibruitnib initiation) |
|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 85 | 1 | 15 | 4 | No | No | B-blocker, Sartan | AF | PDR (1.5) and tox-DTD (4.7) |
| **2** | 77 | 0 | 5 | 4 | Valvulopathy | No | No | AF | PDR (5.6) and tox-DTD (17) |
| **3** | 74 | 0 | 10 | 4 | Valvulopathy | No | No | AF | PDR (4) |
| **4** | 85 | 1 | 12 | 6 | Valvulopathy | NAO | No | AF | PDR (2.7) and tox-DTD (16.5) |
| **5** | 72 | 1 | 8 | 2 | Myopathy | Cardioaspirin | No | AF | Tox-DTD (2.7) |
| **6** | 76 | 1 | 5 | 5 | No | Cardioaspirin | ACEi | AF | Tox-DTD (4) |
| **7** | 78 | 1 | 2 | 3 | No | No | No | Sudden death | Tox-DTD (2.9) |
| **8** | 78 | 2 | 9 | 10 | No | Cardioaspirin | Sartan | AF | Tox-DTD (4.1) |
| **9** | 87 | 2 | 9 | 5 | Valvulopathy | No | B-blocker+furosemide | AF+cardiac failure | Tox-DTD (5) |
| **10** | 79 | 0 | 6 | 7 | No | No | No | AF | Tox-DTD (1.3) |
| **11** | 76 | 2 | 13 | 19 | No | No | No | AF | Tox-DTD (11.3) |
| **12** | 66 | 0 | 7 | 15 | No | No | Ca-antagonist | AF | Tox-DTD (13.5) |
| **13** | 63 | 0 | 8 | 10 | Arrhythmia | No | Flecainide, B-blocker, Sartan | AF | PDR (19.3) and tox-DTD (22.6) |
| **14** | 72 | 0 | 8 | 12 | Arrhythmia | No | Flecainide | AF | PDR (35.1) |
| **15** | 79 | 1 | 6 | 5 | No | No | No | Tachy/Brady syndrome | Tox-DTD (10.2) |
| **16** | 71 | 1 | 8 | 4 | No | No | ACEi + Ca-antagonist +statine | AF | PDR (17.4) and tox-DTD (18.3) |
| **17** | 72 | 1 | 4 | 3 | No | No | Ca-antagonist | Atrial flutter | PDR (2.7) |
| **18** | 68 | 1 | 4 | 2 | No | Cardioaspirin | Ca-antagonist | ACS | Tox-DTD (58.1) |
| **19** | 49 | 0 | 0 | 0 | No | No | No | ACS | PDR (15.3) |
| **20** | 70 | 1 | 3 | 2 | No | No | No | AF | Tox-DTD (1.6) |
| **21** | 48 | 0 | 1 | 0 | No | No | No | Ventricular arrhythmia | Tox-DTD (9.9) |
| **22** | 78 | 0 | 3 | 4 | No | No | Ca-antagonist | ACS | Tox-DTD (25) |
| **23** | 76 | 1 | 3 | 1 | No | No | No | AF secondary to acute pericarditis. Subsequent anticoagulant-related massive pericardial hemorrhage | PDR (21.8) and Tox-DTD (23.4) |
| **24** | 66 | 0 | 0 | 0 | No | No | No | Non-sustained ventricular tachycardia | Tox-DTD (3.9) |
| **25** | 58 | 0 | 2 | 0 | No | No | No | AF + cardiac failure | PDR (34.3) |
| **26** | 82 | 2 | 8 | 2 | Arrhythmia | NAO | B-blocker, Sartan | AF | PDR (4.9) |

***At ibrutinib initiation;**

**AE, Adverse Event; tx, therapy; B-blocker, beta-blocker; Ca-antagonist, calcium antagonist; ACEi, Angiotensine Converting Enzyme inhibitor; AF, Atrial Fibrillation; ACS, Acute Coronary Syndrome**