Current Evidence For Dose Modifications Based On Available Tools In Older Cancer Patients

Dr. Tara Chand Gupta

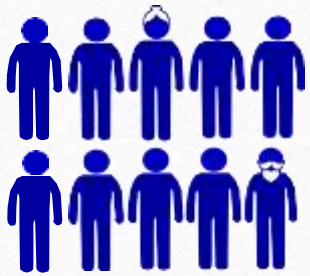
Consultant Medical Oncology

BMHRC, Jaipur

A CRYSTAL CLEAR OBSERVATION

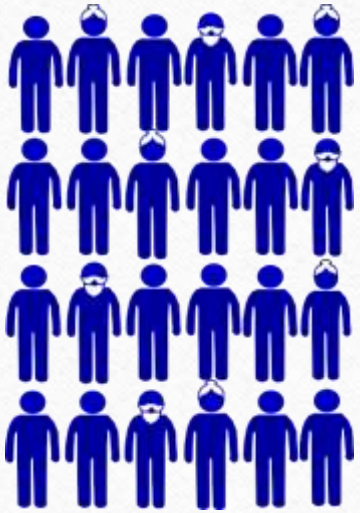
New cases of cancer

2012



1/3 patients ≥ 75 yrs

2050



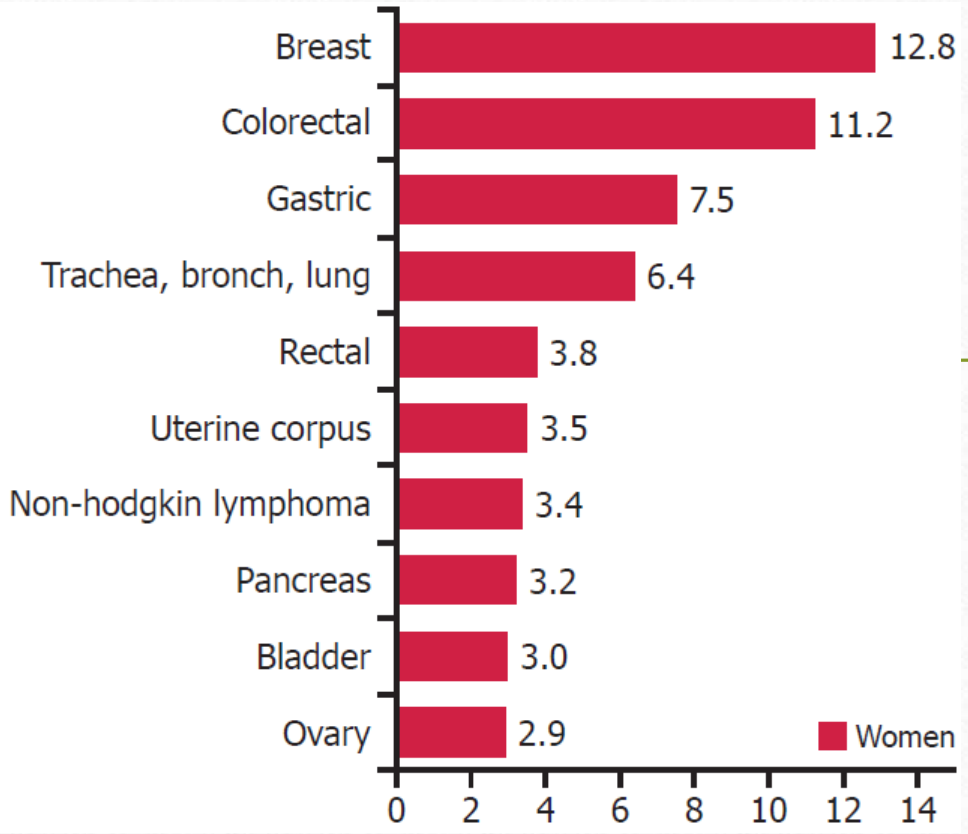
1/2 patients ≥ 75 yrs

Silver tsunami is coming

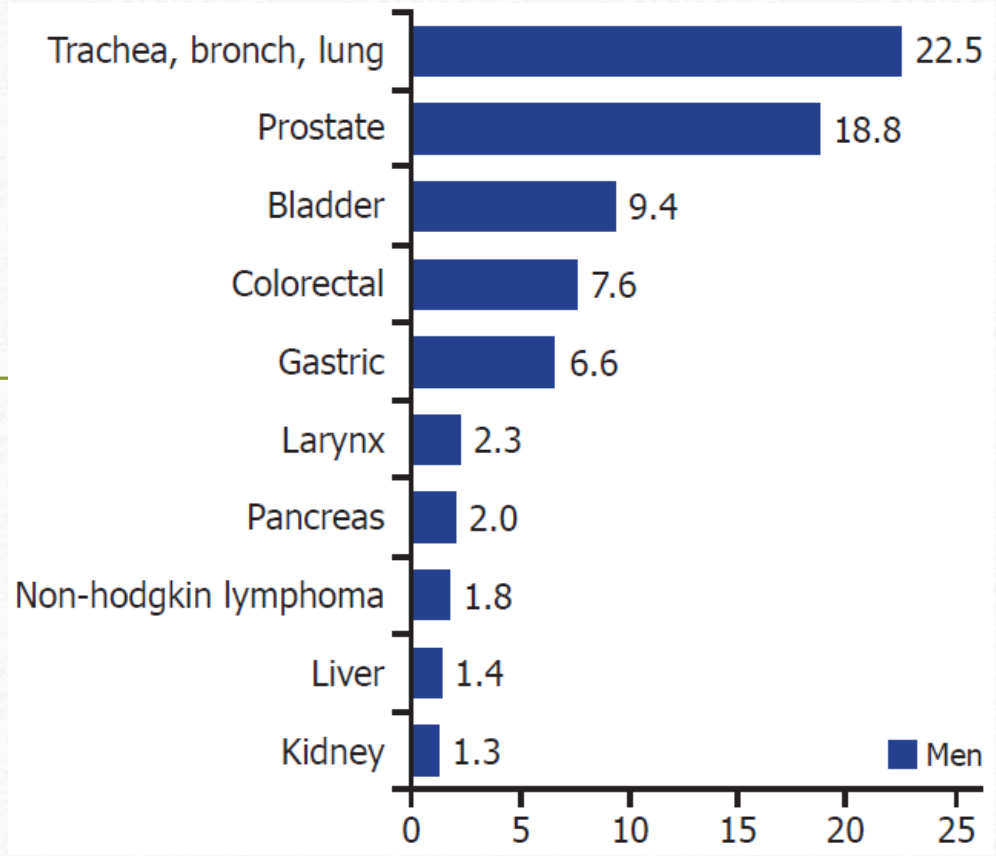
Kendal WS. Cancer 2009
French National Cancer Institute 2014

Most frequently seen cancer types

Women aged ≥ 70 years



Men aged ≥ 70 years



1. Cinar D, Dilaver Tas D. Cancer in the elderly. North Clin Istanb. 2015; 2(1): 73–80.

WE'VE MADE PROGRESS

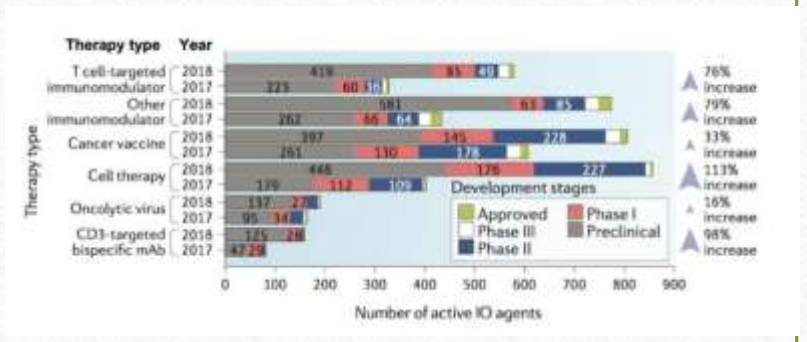
Chemotherapy
Endocrine therapy

Targeted therapies and personnalized medicine

Immunotherapy Immune Checkpoint Inhibitors

Epidrugs

New Drugs
-CART cells
-Bispecific Antibodies
-Cytokines



1900s 2000 2010 2020

Tang et al. Nature Drug Discover 2018

DOES EVERYONE BENEFIT FROM SYSTEMIC TREATMENTS ?

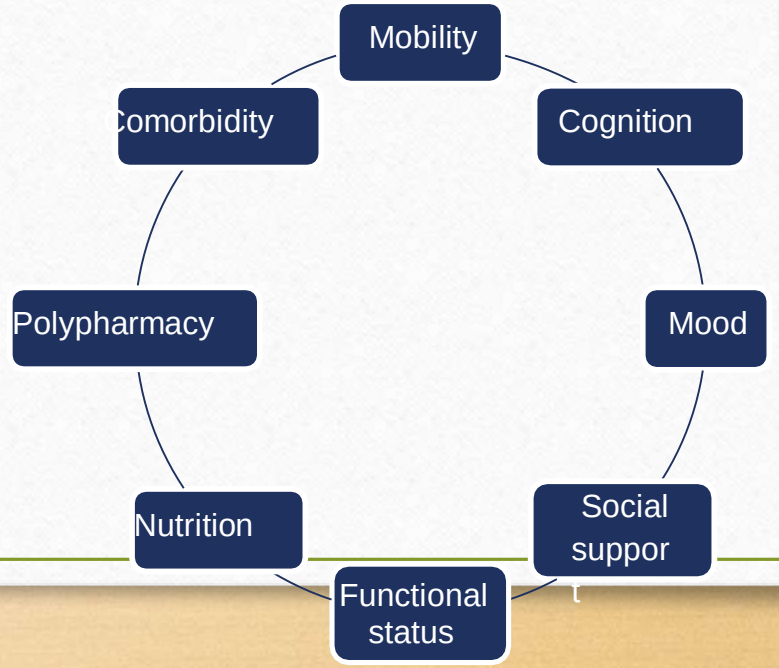
Heterogeneous population

Fit
ECOG PS 0-1
Clinical trial population

Frail
ECOG PS 2-3
Real life population

Screening tools

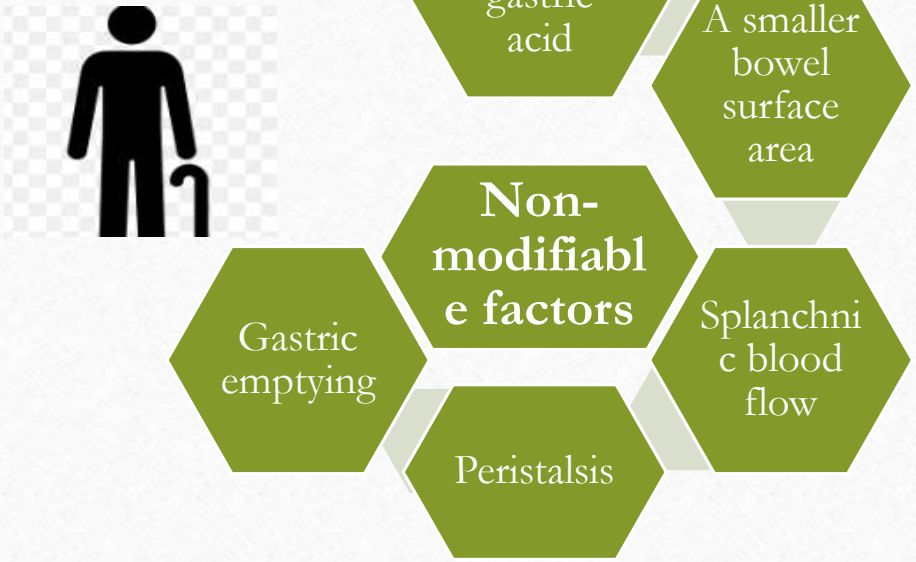
Geriatric Assessment



Pharmacokinetics drug absorption in older adults

Pharmacokinetics is defined as the time course of a drug (and/or drug metabolites) throughout the body about absorption, distribution, metabolism, and excretion/elimination.

Pharmacokinetics drug absorption can be affected by non-modifiable and modifiable factors in older adults



Modifiable factors

Polypharmacy

Concomitant medication use with drugs that alter absorption of oncology agents (e.g., erlotinib absorption can be significantly reduced by proton pump inhibitors such as omeprazole)

Gastrointestinal physiologic changes have the potential to generate significant concern with the exponential growth and expansion of oral oncology therapies.

Influence of aging on pharmacokinetic parameters

Absorption

Distribution

Metabolism

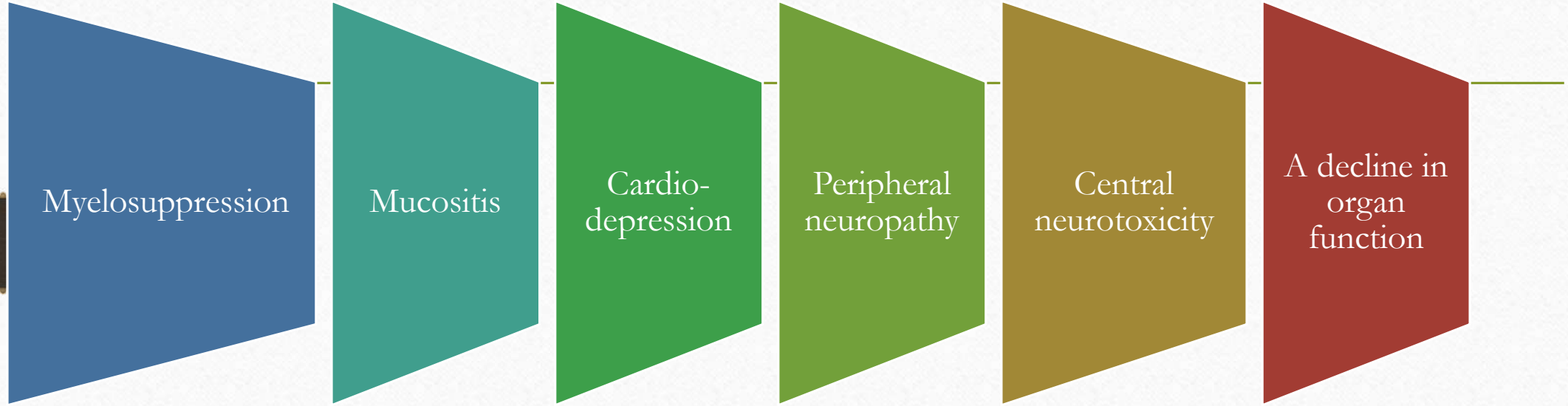
Elimination

Parameter	Direction	Effect on Exposure
Gastrointestinal pH	↑	↓↑
Gastric emptying time	↑	↓
Motility	↓	↓
Splanchnic blood flow	↓	↓
Absorptive surface	↓	↓
Body composition		
Body fat	↑	↑*
Plasma volume	↓	↑§
Total body water	↓	↑§
Intra-/extracellular body fluid	↓	↑§
Plasma proteins		
Serum albumin	↓	↑FF
Bilirubin	↓	↑FF
Erythrocytes	↓	↑FF
Serum α1-acid glycoprotein	↑	↓FF
Hepatic blood flow	↓	↑
Hepatic mass	↓	↑
CYP P450 enzymes	0/↓	(↑)
Renal blood flow/glomerular filtration	↓	↑
Tubular secretion	↓	↑

* For lipophilic drugs; § for hydrophilic drugs; FF = free fraction

Greater risk of cytotoxic chemotherapy in elderly

- Complications of cytotoxic chemotherapy are more common in older patients (65 years of age and older) with cancer than in younger patients because of the following reasons -



Prospective trials in older patients with lymphoma or solid tumors have found that age is a risk factor for chemotherapy-induced neutropenia and its complications. [1,2]

Effective management of the toxicity associated with chemotherapy with appropriate supportive care is crucial, especially in the elderly population, to give them the best chance of cure and survival, or to provide palliation.

Geriatric Domains

1. Assessment Of Function - IADL
2. Comorbidity, -History or Validated tool
3. Falls, - Single question for fall
4. Depression, -Geriatric Depression Scale
5. Cognition, - BOMC or Mini Cog
6. And Nutrition. - Unintentional Weight loss

Integrated tools

1. CARG
2. CRASH
3. G8
4. VES 13
5. ePrognosis – Shoenberg's & Lee

Geriatric oncology tools: Assessment of function

Instrumental activity of daily living (IADL)

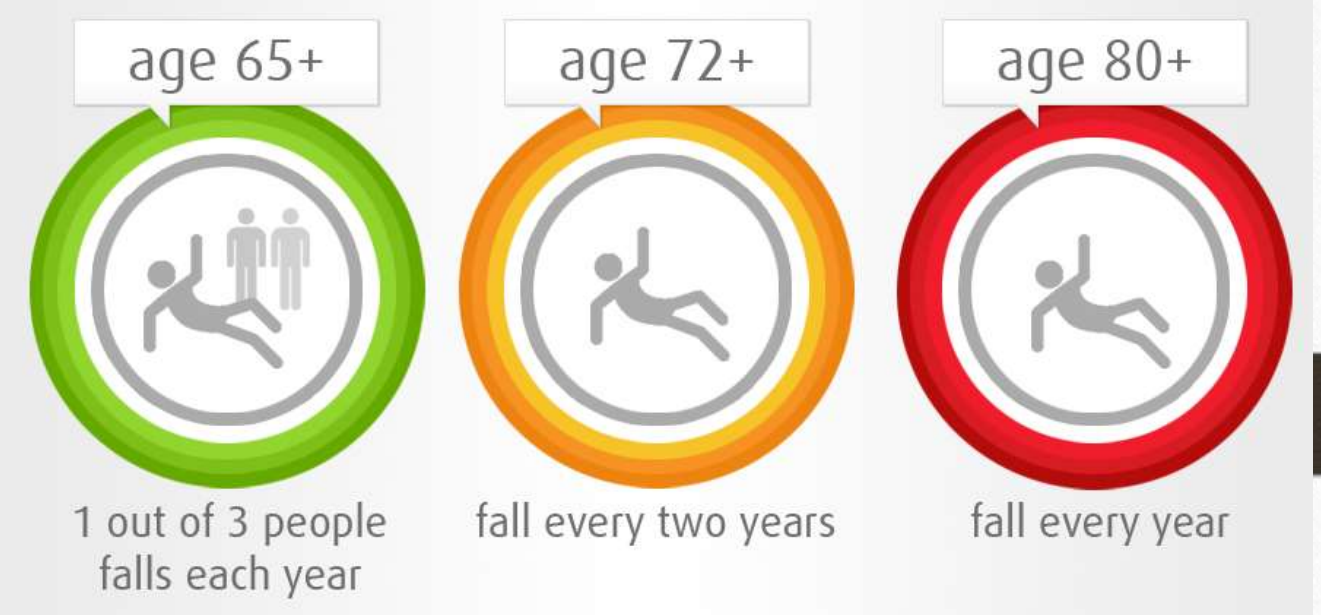
- Measures ability to complete activities required to maintain independence in the community (shopping, meal preparation, making telephone calls, money management)
- Dependence on any task signifies impairment.
- IADLs predict chemotherapy toxicity, mortality, hospitalizations, and functional decline.
- No of items – 7
- Range of scores: 0-14 (higher score: less need for assistance)

Tool	Description	Abnormal score (range)
Katz Activities of Daily Living	6-item tool to assess basic activities of daily living	≤ 5 (0–6)
Lawton Instrumental Activities of Daily Living	8-item tool to assess activities of daily living needed to live independently	≤7 (0–8)
Timed up and go test	Time it takes a patient to stand up from a chair (without using their arms), walk 3 metres, turn around, and return to the chair and sit down.	> 12s

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
2. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.
3. Hernandez Torres C, Hsu T. Comprehensive Geriatric Assessment in the Older Adult with Cancer: A Review. Eur Urol Focus. 2017 Oct;3(4-5):330-339.

Geriatric oncology tools:Assessment of falls

- Indicates number of times fallen in the last 6 months.
- Falls have been associated with chemotherapy toxicity.
- Single Item.



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Geriatric oncology tools:Assessment of comorbidity

- Presence/absence of 13 comorbid illnesses.
- Robust review of chronic medical conditions and medications through routine history: three or more chronic health problems or one or more serious health problems.
- Comorbidity is associated with poorer survival, chemotherapy toxicity, mortality, and hospitalizations.

Tool	Description	Abnormal score (range)
Charlson Comorbidity Index	Assess for presence of 19 comorbid conditions weighted for severity	≥1
Charlson Comorbidity Index (updated index)	Assess for presence of 12 comorbidities	≥1
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)	14-item tool; score based on severity of each comorbid condition, graded from 0 to 4	(0-56)
Adults Comorbidity Evaluation- 27 (ACE-27)	27-item; score based on severity of each comorbid condition, graded from 0–3	Overall comorbidity score ranges from 0 (none) to 3 (severe)

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
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Geriatric oncology tools: Assessment of cognition

- Mini-Cog: an abnormal test is defined by zero words recalled. OR
- One to two words recalled + abnormal clockdrawing test. This screening test for cognitive impairment and abnormal scores requires further follow-up and decision-making capacity assessment. OR
- BOMC test: a score of 6 or greater identifies patients who have moderate deficits, and a cut point of 11 or greater identifies patients with severe cognitive impairment.

- Cognitive impairment is associated with poorer survival in older patients with cancer and increased chemotherapy toxicity risk.

Tool	Description	Abnormal score (range)
Mini Mental Status examination (MMSE)	11-item test that includes registration, attention and calculation, recall, language, and orientation	≤23 (0–30)
Montreal Cognitive Assessment (MOCA)	12-item test of cognitive function; assesses short term memory, visuospatial awareness, executive function, attention, and orientation.	<26 (0-30)
Mini-Cog	Cognitive screen that includes a recall test and clock drawing	<3 (0-5)
Blessed Orientation Memory Concentration test	6-item tool that tests orientation, attention and memory	>10 (0-12)

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
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Geriatric oncology tools: Assessment of depression

- GDS 15 item: a score of > 5 suggests depression and requires follow-up.
- Depression has been associated with unexpected hospitalizations, treatment tolerance, mortality, and functional decline in older adults with cancer receiving chemotherapy.
- Other evaluation options:
  - ✓ GDS recommended also by ASCO guidelines for depression.
  - ✓ The Patient Health Questionnaire-9 is an alternative and is also recommended by ASCO guidelines for depression.
  - ✓ The mental health inventory is an option and has been associated with outcomes in older patients with breast cancer.

Tool	Description	Abnormal score (range)
Geriatric Depression Scale	15-item self-assessment with yes/no questions used to identify older patients at risk of depression	>5 (0-15)
Hospital Anxiety and Depression Scale	14-item self-assessment of anxiety (7 items) and depression (7 items)	>8 (0–21) for depression and anxiety subscales

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
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Geriatric oncology tools: Assessment of nutrition

- Unintentional weight loss; >10% weight loss from baseline weight); BMI < 21 kg/m^2
- Poor nutrition is associated with mortality in older patients with cancer.
- Other evaluation options:
  - ✓ Consider G8 and MNA as alternatives; both are associated with mortality in older patients with cancer.

Tool	Description	Abnormal score (range)
Mini Nutritional Assessment	6-item tool to identify patients at risk of malnutrition	<24 (0-30)

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
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3. Hernandez Torres C, Hsu T. Comprehensive Geriatric Assessment in the Older Adult with Cancer: A Review. Eur Urol Focus. 2017 Oct;3(4-5):330-339.

Why Not PS Alone ?

The Phase III Randomized ESOGIAGFPC- GECP 08-02 Study

Elderly patients ≥ 70 years old with a PS of 0 to 2 and stage IV NSCLC

Chemotherapy allocation based on PS and age

Treatment allocation based on CGA

Treatment and Outcomes

Treatment and Outcome	Standard Arm (n = 251)	CGA Arm (n = 243)	*P* (Log-Rank Test)
Treatment allocation, No. (%)			< .001
Monotherapy	163 (64.9)	76 (31.3)	
Doublet	88 (35.1)	111 (45.7)	
BSC		56 (23.0)	
Median TFFS, months			.32
All	3.2	3.1	
Doublet	4.4	4.8	
Monotherapy	2.9	2.6	
BSC	—	1.3	
Reasons for treatments failures, No. (%)			
Missing data	14	15	
Progression	156 (65.8)	158 (69.3)	.42
Toxicity	28 (11.8)	11 (4.8)	.01
Toxicity except for BSC in the CGA arm	28 (11.8)	11 (6.3)	.06
Withdrawal of consent	9 (3.8)	7 (3.1)	.67
Death	31 (13.1)	32 (14.0)	.76
Other	13 (5.5)	20 (8.8)	.17
Median PFS, months			.59
All	3.7	3.4	
Doublet	4.7	4.8	
Monotherapy	3.1	2.7	
BSC	—	1.3	
Median OS, months			.87
All	6.4	6.1	
Doublet	8.6	10.0	
Monotherapy	5.7	4.9	
BSC	—	2.8	
Mean life expectancy adjusted on QoL, months	4.3	4.4	.51

Abbreviations: BSC, best supportive care; CGA, comprehensive geriatric assessment; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TFFS, treatment failure–free survival.

Patients in the CGA arm, compared with standard arm patients, experienced significantly less all grade toxicity (85.6% v 93.4%, respectively P = .015) and fewer treatment failures as a result of toxicity (4.8% v 11.8%, respectively; P = .007).

In elderly patients with advanced NSCLC, treatment allocation based on CGA failed to improve the TFFS or OS but slightly reduced treatment toxicity.

Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study

C. Kenis, D. Bron, Y. Libert, L. Decoster

Background: To evaluate the large-scale feasibility and usefulness of geriatric screening and assessment in clinical oncology practice by assessing the impact on the detection of unknown geriatric problems, geriatric interventions and treatment decisions.

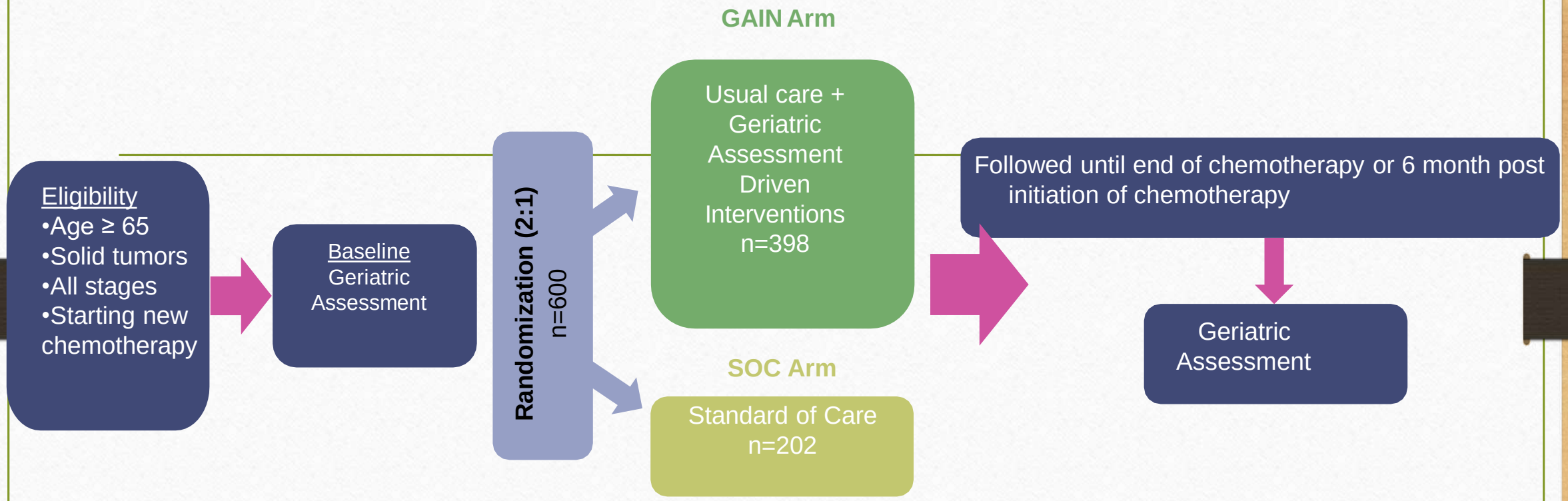
Patients and methods: Eligible patients who had a malignant tumour were ≥70 years old and treatment decision had to be made. Patients were screened using G8; if abnormal (score ≤14/17) followed by Comprehensive Geriatric Assessment (CGA). The assessment results were communicated to the treating physician using a predefined questionnaire to assess the topics mentioned above.

Results: One thousand nine hundred and sixty-seven patients were included in 10 hospitals. Of these patients, 70.7% had an abnormal G8 score warranting a CGA. Physicians were aware of the assessment results at the time of treatment decision in two-thirds of the patients ($n = 1115$; 61.3%). The assessment detected unknown geriatric problems in 51.2% of patients. When the physician was aware of the assessment results at the time of decision making, geriatric interventions were planned in 286 patients (25.7%) and the treatment decision was influenced in 282 patients (25.3%).

Conclusion: Geriatric screening and assessment in older patients with cancer is feasible at large scale and has a significant impact on the detection of unknown geriatric problems, leading to geriatric interventions and adapted treatment.

Key words: cancer, elderly, geriatric assessment, treatment decision

IMPACT OF GA ON CHEMOTOXICITY- GAIN Study



Primary endpoints:
- Incidence of grade 3-5 chemotoxicity

Secondary endpoints:
- Advance directive completion
- Unplanned hospitalizations
- ER visits
- Average length of stay

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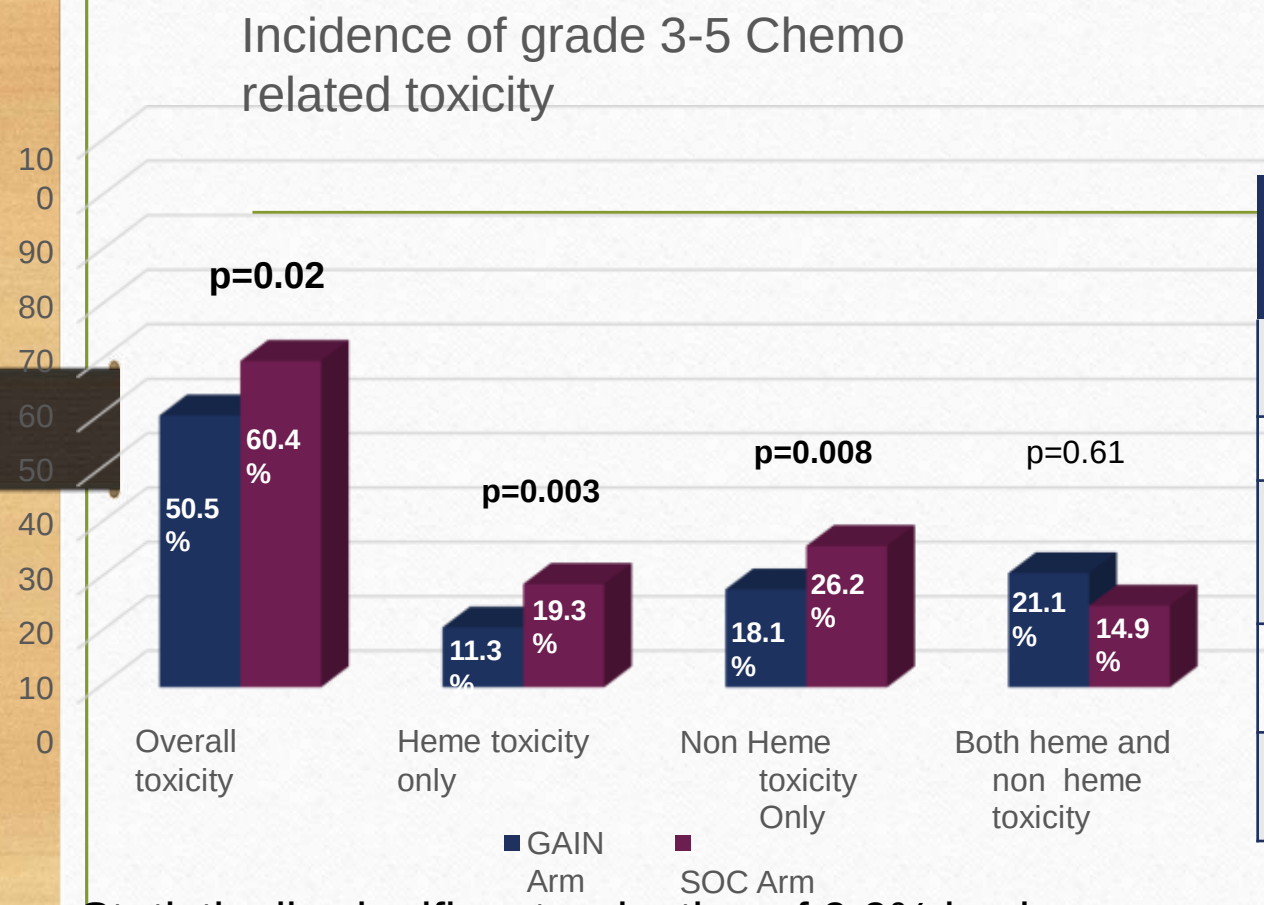
GAIN - Results



Statistically significant reduction of 9.9% in chemo-related toxicity compared to the SOC Arm

Secondary endpoints

	GAIN Arm n (%)	SoC Arm n (%)	p-value
Advanced directive completion	**278 (70%)**	**119 (59%)**	**<0.01**
ER visits for chemotox	109 (27%)	62 (31%)	0.40
Hospitalizations due to grade 3+ chemotox	88 (22%)	39 (19%)	0.43
Hospitalizations due to grade 4+ chemotox	19 (22%)	14 (36%)	0.09
Average Length of stay [median (range)]	4.8 (1-23	5 (1.7-26)	0.60

Satistically significant increase in AD completion

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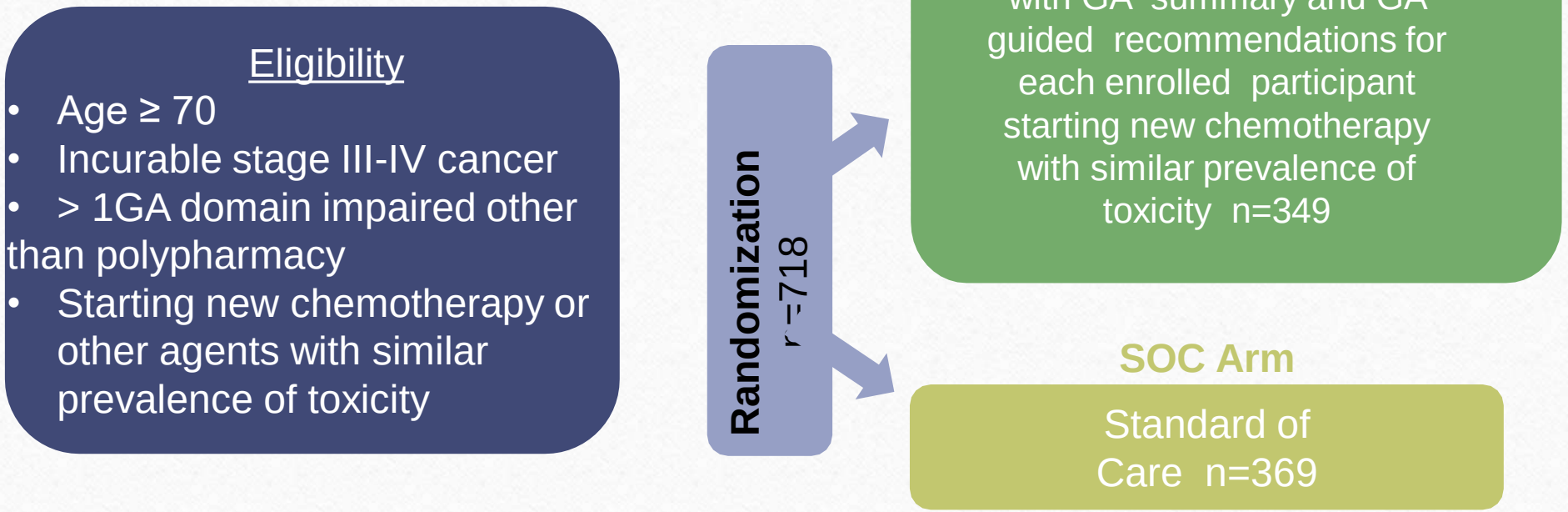
GAP-70



Endpoints:

- Clinician-rated grade 3-5 toxicity
- Survival at 6 months
- Treatment decisions
- Functional and physical decline
- Patient reported toxicities

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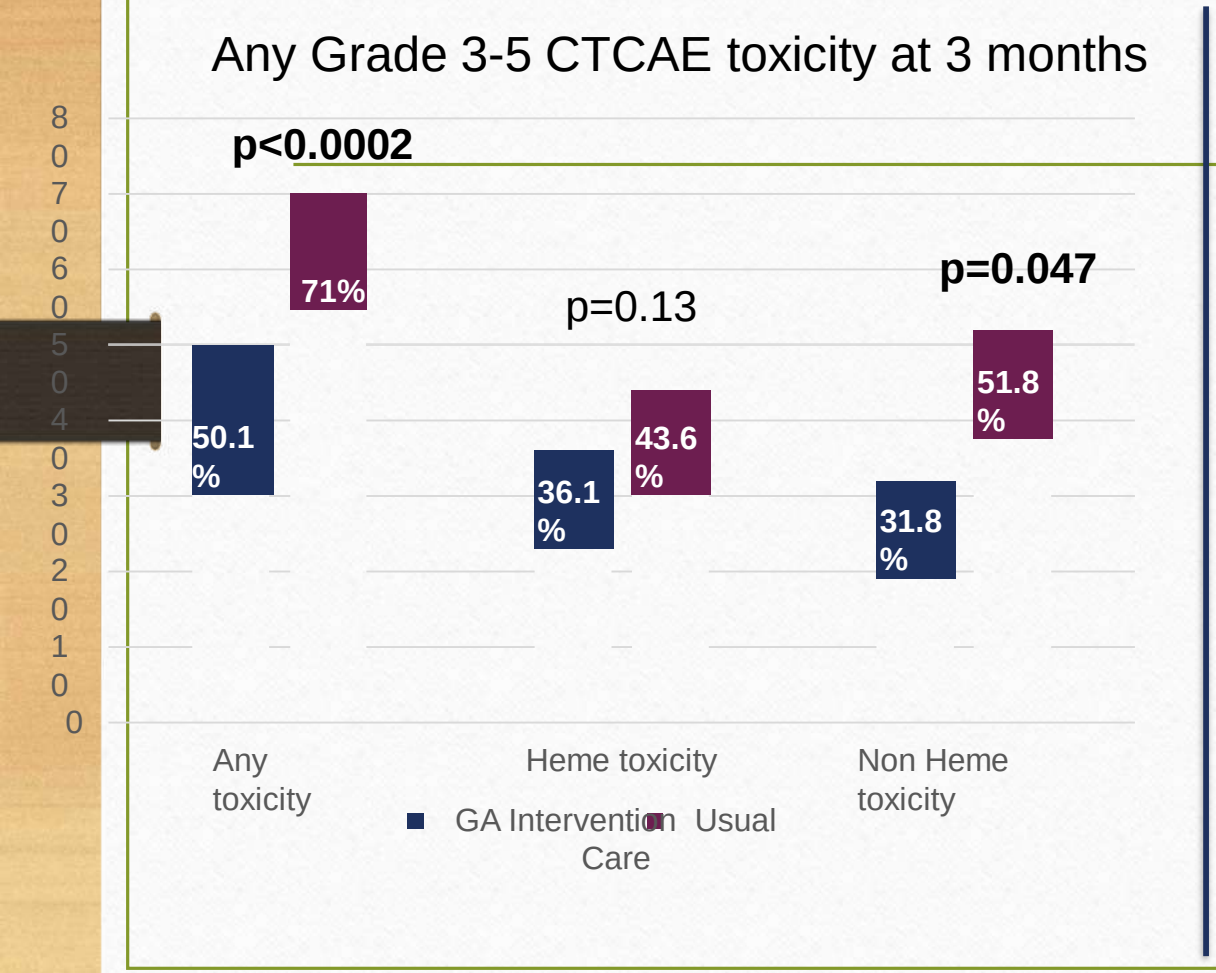
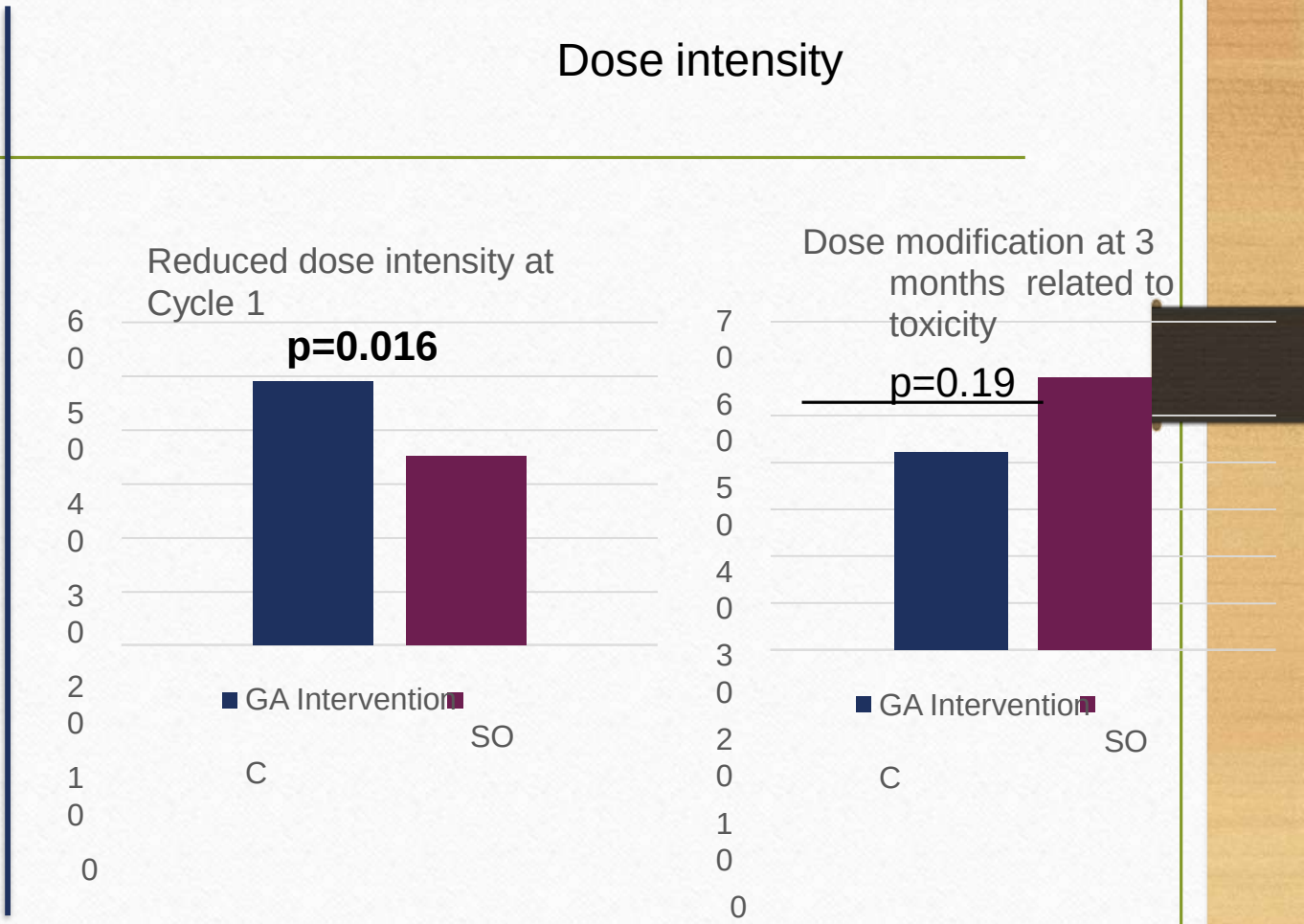
GAP-70- Results





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Geriatric oncology tools: Risk of chemotherapy toxicity (CARG)

- CARG toxicity tool: provides estimates for overall risk of grade 3 to 5 chemotherapy toxicity.

Table 1. Cancer and Aging Research Group (CARG) Variables and Scoring

Variable	Score
Age ≥ 72 years old	2
Cancer type (gastrointestinal or genitourinary)	2
Chemotherapy dosing (standard dosing)	2
Number of chemotherapy drugs (polychemotherapy)	2
Hemoglobin (< 11 g/dL in males; < 10 g/dL in females)	3
Creatinine clearance (< 34 mL/min)	3
Hearing (fair or worse)	2
Number of falls in the past 6 months (one or more)	3
Take medications with some help/unable	1
Walking one block, somewhat limited/limited a lot	2
Decreased social activity because of physical/emotional health problem (limited at least sometimes)	1

Note. Information from Hurria et al. (2011).

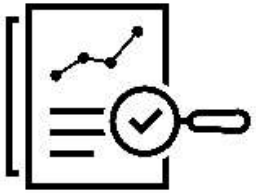
Table 2. Total Risk Score for the Cancer and Aging Research Group (CARG) Tool

	Total risk score	% Risk	N
Low	0–3	25%	28
	4–5	32%	100
Mid	6–7	50%	136
	8–9	54%	91
High	10–11	77%	62
	12–19	89%	47

Note. Information from Cancer and Aging Research Group (n.d.-a). Table used with permission.

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
2. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.
3. Schiefen JK, Madsen LT, Dains JE. Instruments That Predict Oncology Treatment Risk in the Senior Population. J Adv Pract Oncol. 2017 Jul-Aug;8(5):528-533.

Predicting toxicity in older adults- A prospective multicentre study



- 500 patients aged ≥65 years with cancer from seven institutions completed a prechemotherapy assessment that captured sociodemographics, tumor/treatment variables, laboratory test results, and geriatric assessment variables.
- Patients were followed through the chemotherapy course to capture grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (death) as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events.

1. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.

Predictors of Toxicity

- Age ≥ 72 years

Age

- GI/GU Cancer
- Chemotherapy dosing, standard dose
- Polychemotherapy

Tumor/Treatment variables

- Hemoglobin (Male <11 g/dL, Female <10 g/dL)
- Creatinine Clearance (Jelliffe-ideal wt<34)

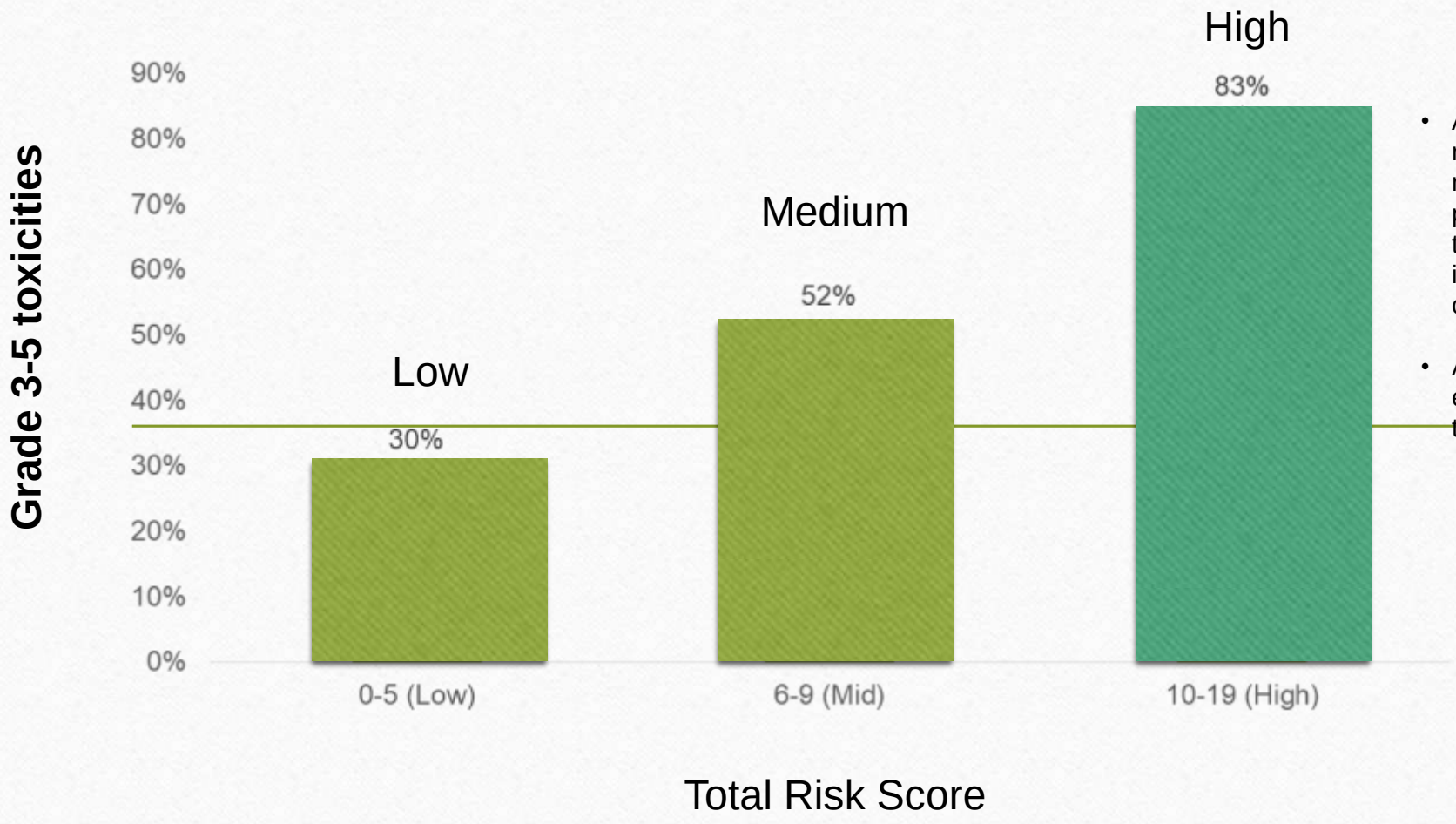
Laboratory values

- Fall(s) in last 6 months, 1 or more
- Hearing impairment (fair or worse)
- Limited in walking 1 block (MOS)
- IADL: Taking medication with some help/unable
- Decreased social activity because of physical/emotional health, limited at least sometimes

Geriatric Assessment

1. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.

Risk of toxicity by total score



- A scoring system in which the median risk score was 7 (range, 0 to 19) and risk stratification schema (risk score: percent incidence of grade 3 to 5 toxicity) identified older adults at low, intermediate, or high risk of chemotherapy toxicity ($P < 0.001$).
- A risk stratification schema can establish the risk of chemotherapy toxicity in older adults.

1. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.

Geriatric oncology tools: Risk of chemotherapy toxicity (CRASH)

- CRASH tool: provides estimates separately for risk of grade 3 hematologic and grade 3 to 4 nonhematologic toxicity.
- Assessment of risk of hematologic toxicity includes
  - *Diastolic blood pressure (>72 mm Hg)*
  - *IADL score (<26)*
  - *LDH (>459 U/L)*
- Assessment of risk of nonhematologic toxicity includes
  - *ECOG PS,*
  - *MMSE (<30)*
  - *MNA (<28).*
- Chemotherapy intensity is assessed with MAX2 index.
- The CRASH scale includes GA measures known also to predict other adverse outcomes, such as mortality, functional decline, and hospitalizations: IADLs, MMSE, and MNA.

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
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Predicting the risk of toxicity: CRASH score

- Extermann M et al conducted prospective, multicentric study of patients aged ≥ 70 years who were starting chemotherapy. 518 patients were evaluable and were split randomly (2:1 ratio) into a derivation cohort and a validation cohort.
- CRASH score was conducted along 2 subscores: Heme toxicity and Non Heme toxicity.
- Predictors of H toxicity were lymphocytes, aspartate aminotransferase level, Instrumental Activities of Daily Living score, lactate dehydrogenase level, diastolic blood pressure and Chemotox
- Predictors of NH toxicity were hemoglobin, creatinine clearance, albumin, selfrated health, Eastern Cooperative Oncology Group performance, Mini-Mental Status score, Mini-Nutritional Assessment score and Chemotox

1. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012 Jul 1;118(13):3377-86.

Predicting the risk of toxicity: CRASH score

Predictors	0 points	1 point	2 points
Hematologic score			
Diastolic BP	≤ 72	>72	
IADL	26-29	10-25	
LDH	0-459		>459
Chemotox	0-0.44	0.45 to 0.57	>0.57
Non-hematologic score			
ECOG Performance Status	0	1-2	3-4
Mini Mental Status Examination	30		<30
Mini Nutritional	28-30		<28
Chemotox	0 – 0.44	0.45 – 0.57	>0.57

1. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012 Jul 1;118(13):3377-86.

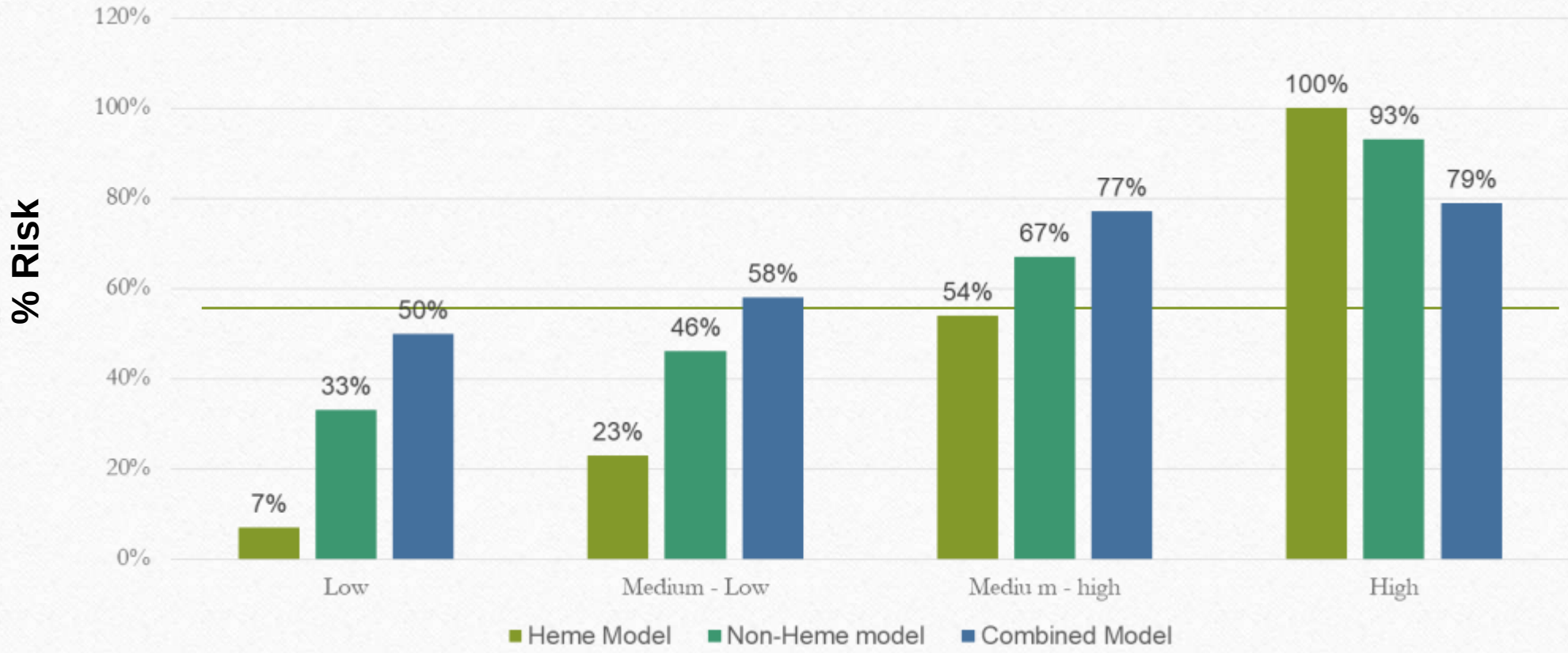
Predicting the risk of toxicity: CRASH score

Table 4. Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Scoring Analysis (Individual Risk)

	CRASH score (points: % with severe toxicity)			
Sample	**Hematologic subscore**	**Nonhematologic subscore**	**Combined score**	**Risk category**
Derivation (n = 347)	0–1: 7%	0–2: 33%	0–3: 50%	Low
	2–3: 23%	3–4: 46%	4–6: 58%	Intermediate-low
	4–5: 54%	5–6: 67%	7–9: 77%	Intermediate-high
	> 5: 100%	> 6: 93%	> 9: 79%	High
Validation	0–1: 12%	0–2: 42%	0–3: 61%	
	2–3: 35%	3–4: 59%	4–6: 72%	
	4–5: 45%	5–6: 66%	7–9: 77%	
	> 5: 50%	> 6: 100%	> 9: 100%	

1. Schiefen JK, Madsen LT, Dains JE. Instruments That Predict Oncology Treatment Risk in the Senior Population. J Adv Pract Oncol. 2017 Jul-Aug;8(5):528-533.

CRASH Model – Risk Categories



1. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012 Jul 1;118(13):3377-86.

MAX2

The goal of the MAX2 approach is to define the average published risk of a patient experiencing severe toxicity from chemotherapy.

Severe toxicity is defined as grade 4 hematologic (H) toxicity and/or grade 3-4 non-hematologic (NH) toxicity by CTCAE criteria (presently version 3), or similar classification using the same grading of neutropenia.

The MAX2 index[a]

$$\frac{\text{Most frequent grade 4 haematological toxicity} + \text{most frequent grade 3+4 non-haematological toxicity}}{2}$$

Example

25% grade 4 neutropenia $\text{MAX2} = \frac{0.25 + 0.13}{2} = 0.19$
13% grade 3+4 diarrhoea

Notes

Alopecia is not counted

When only white blood cell nadirs are reported, ANC is extracted as follows:

0.6* G3+4 leucopenia, if G4 leukopenia <30%

0.8* G3+4 leucopenia, if 30% and above

[a] An index that allows adjustment for the toxicity of different chemotherapy regimens for comparison [3].

Validation results of MAX2

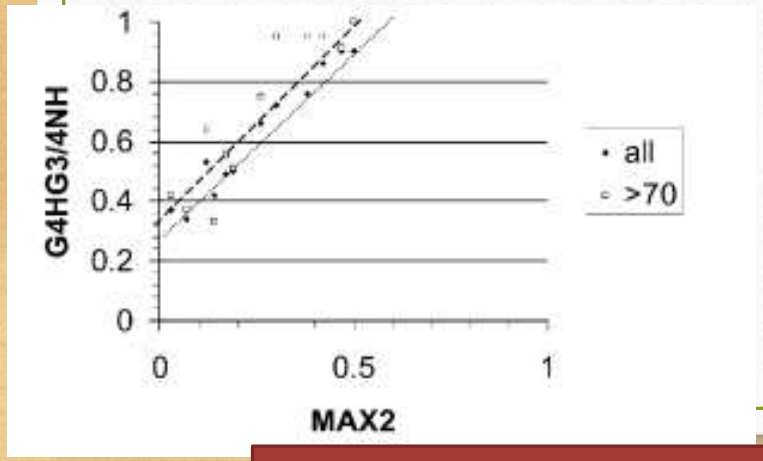
The MAX2 of each regimen and the percentage of patients experiencing severe toxicity

MAX2 and percentage of patients experiencing severe toxicity

Study	Regimen	MAX2	Risk of toxicity	Risk in patients > 70 years
E1193	Doxorubicin	0.26	0.66	0.75
	Paclitaxel	0.42	0.86	0.95
	AT + G-CSF	0.30	0.72	0.95
E2290	5-FU	0.07	0.34	0.37
	PALA-5-FU	0.03	0.37	0.42
	5-FU intravenous	0.17	0.49	0.55
	5-FU-interferon-α-LV orally	0.19	0.50	0.51
	5-FU-LV	0.12	0.53	0.64
E5592	Cisplatin-etoposide	0.38	0.76	0.95
	Cisplatin-paclitaxel 250	0.47	0.90	0.91
	Cisplatin-paclitaxel 135	0.50	0.90	1.00
E6293	Tomudex	0.14	0.42	0.33

AT, doxorubicin-paclitaxel; 5-FU, 5-fluouracil; G-CSF, granulocyte-colony-stimulating factor; LV, leucovorin.

The association of the MAX2 index with the per patient incidence of grade 4 hematological and/or grade 3 or 4 non-hematological toxicity was highly significant, both for the overall group and for the elderly subgroup



The results of fitting a simple linear-regression model to the individual observations to describe the association between MAX2 and the incidence of severe toxicity.

MAX2 is a useful tool for the assessment for chemotoxicity and can be used in the future

G-8 screening tool

It was developed to identify elderly cancer patients who would benefit from comprehensive geriatric assessment (CGA).

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m²)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
H	Takes more than 3 medications per day	0 : yes
		1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	**0 – 17**

It should be noted that the G-8 tool is not aimed at replacing expertise of geriatricians for the diagnosis of frailty. Rather, it should be used as a screening tool to identify patients in need for a further assessment and appropriate care.

Total Score : 0-17
Abnormal ≤14

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
2. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.
3. https://www.evidencio.com/models/show/1045

Effectiveness of geriatric screening tool (G8)

Sensitivity and specificity of the G8 tool

Objective	%	95% confidence interval
Sensitivity	77.78%	52.36% to 93.59%
Specificity	81.25%	63.56% to 92.79%
Positive Predictive Value	70.00%	45.72% to 88.11%
Negative Predictive Value	86.67%	69.28% to 96.24%

The grade of concordance between G8 score and the appearance/absence of adverse events were statistically significant (41/50 patients, 82%, p = 0.0002)

Sensitivity resulted in 78% and specificity was 81%; positive predictive value was 70% and negative predictive value was 87%. The most frequent adverse event was arthromyalgia.

Characteristics of patients evaluated with G8

Variable	G8 > 14	G8 ≤ 14	Overall
Number of patients - N	30	20	50
Age in years– Mean (Min-Max)	74,5 (65–86)	77,9 (65–86)	75,1 (65–86)
Any-grade side effects N(%):	4 (13.3)	15 (75)	19 (38)
Arthromyalgia			
G1	2 (6.6)	8 (40)	10 (20)
G2	0	2 (10)	2 (4)
G3	2 (6.6)	2 (10)	4 (8)
G4	0	0	0
Thromboembolic event			
G1	0	0	0
G2	0	0	0
G3	0	0	0
G4	0	1 (5)	1 (2)
Depression			
G1	0	0	0
G2	0	1 (5)	1 (2)
G3	0	0	0
G4	0	0	0
Osteoporosis			
G1	0	0	0
G2	0	0	0
G3	0	1 (5)	1 (2)
G4	0	0	0

In 8 of the 9 patients (88%) who underwent a chemotherapy, there was concordance between G8 and tolerance to endocrine treatment.

The G8 screening tool has a potential role in predicting side effects during a treatment with aromatase inhibitor. G8 could be very useful in everyday clinical practice for this population.

Geriatric oncology tools: Screening (VES 13)

- Thirteen items including age, self-rated health, common functional tasks, and ability to complete physical activities.
- Score of ≥ 3 is associated with mortality and chemotherapy toxicity in older patients with cancer.
- A score of ≥ 7 has been shown to be associated with functional decline.
- VES-13 can also be used as a screening tool to identify older patients who need more comprehensive GA.

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1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
2. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.

Geriatric oncology tools: SPPB and TUG

- Objective physical performance: SPPB, TUG, or gait speed

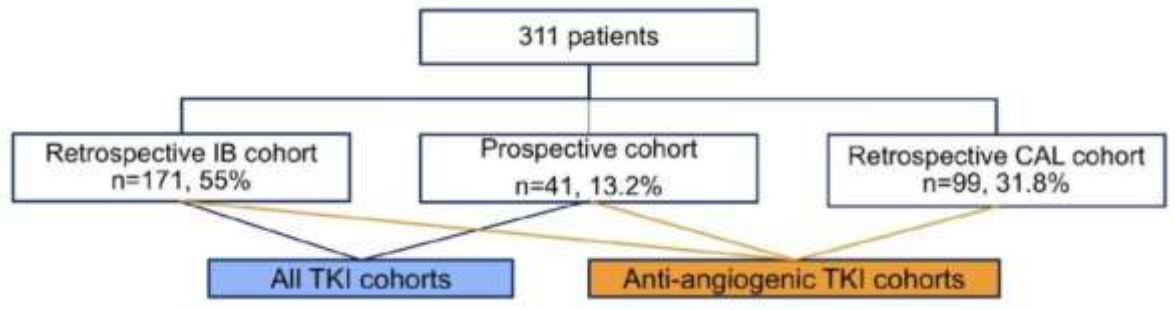
- SPPB includes three tests (balance, chair stands, and gait speed)
- A score of < 9 is associated with increased functional decline, nursing home use, and mortality in community-dwelling older adults.
- In clinical studies, Low SPPB score is associated with increased mortality in older women with gynecologic malignancies.

- TUG measures ability for a patient to get out of a chair and walk 3 m or 10 ft and back
- A score of >12 seconds is associated with an increased risk of falling.
- TUG and gait speed have been shown to be associated with early mortality (6 months) in older patients with cancer receiving chemotherapy.

1. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018 Aug 1;36(22):2326-2347.
2. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011 Sep 1;29(25):3457-65.

TARGETED THERAPIES

- Few dedicated studies
- PreToxE study: retrospective and prospective multicentric study in patients aged 70 years old or over
- Primary end points : incidence of severe toxicity.
- Solid tumors: lung, breast, sarcoma



Multivariate analysis

Variable	Odds ratio	95 % CI		p-value (<0.05)
		Inferior	Superior	
Sex *Female vs male*	1,543	0,870	2,736	0,1378
Age (years) *≥75 vs <75*	1,218	0,687	2,157	0,5001
Concomitant medications *≥ 3 vs <3*	2,088	1,141	3,819	0,0169

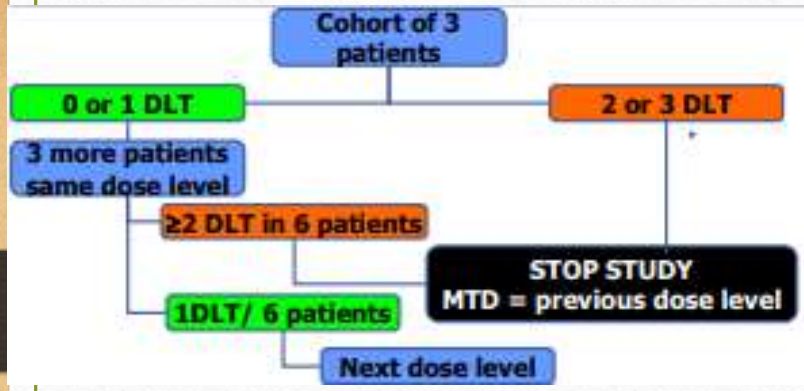
- 41% of ≥ 1 severe toxicity
- Definitive treatment discontinuation: 68.5%
- Persistent or significant disability: 22%

Lebreton C ASCO 2019

VOTRAGE STUDY

VOTRAGE study

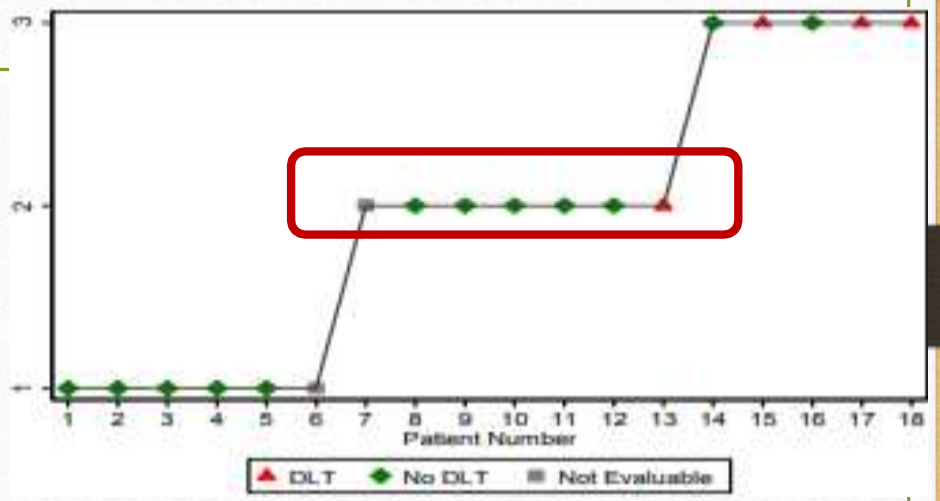
Pazopanib in a population of "frail" elderly patients after geriatric assessment. A phase I study with geriatric criteria



MTD Maximum tolerated dose, DLT Dose limiting toxicity

Dose levels

- **Level -1** 200 mg/j
- **Level 1** 400 mg/j (initial level)
- **Level 2** 600 mg/j
- **Level 3** 800 mg/j



The MTD* is defined as the highest dose level for which 6 patients were treated with a maximum of one patient (~20%) presenting a DLT* during the first month of treatment.

DLT is defined as follow:

- *geriatric criterion*
  Drop of ADL of 2pts or more

hematologic criteria

- *Grade 4 neutropenia more than 5 day or febrile neutropenia more than 1 day*
- *Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding*

non hematologic/non geriatric criteria

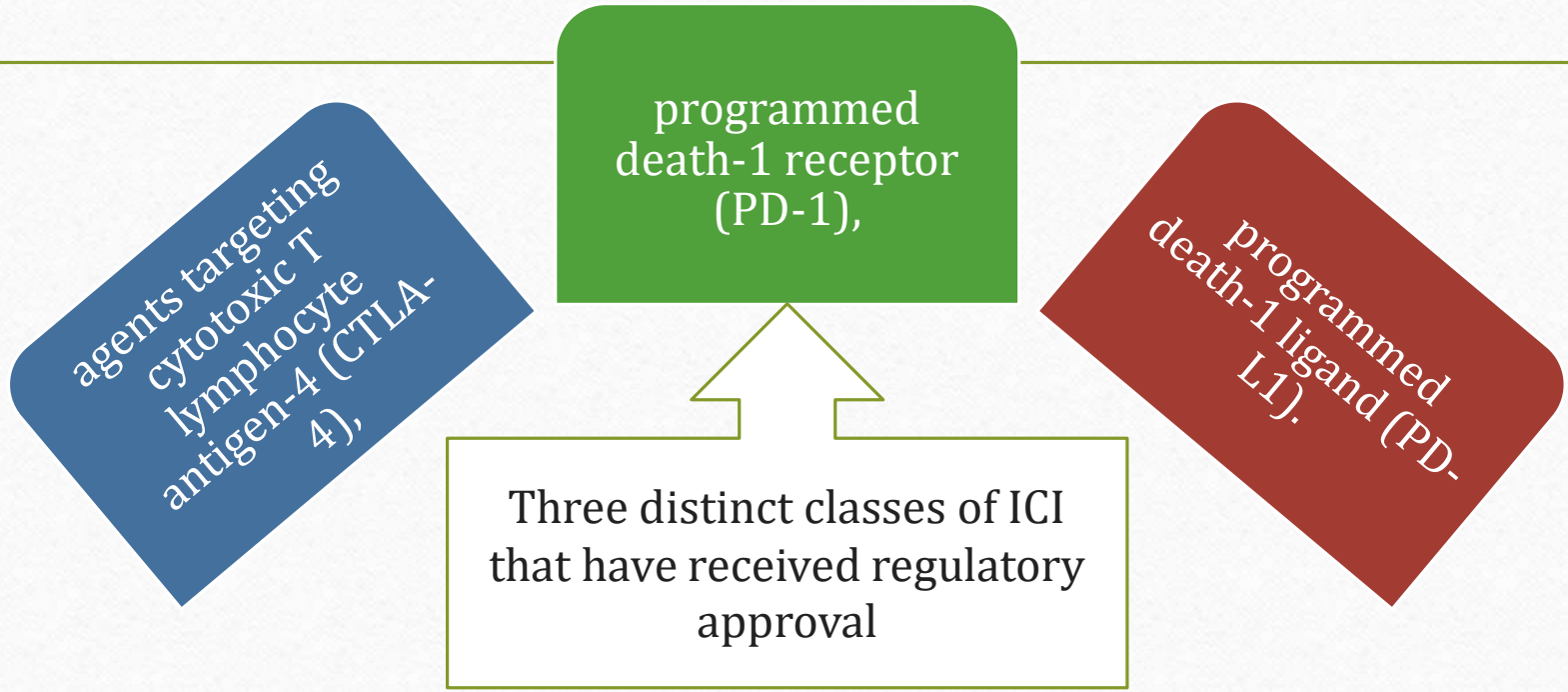
- Grade 4 hypertension
- Delayed treatment (2 weeks) for side effects
- Grade 4 hypophosphatemia
- Grade 3 lipase (> 2N)
- Grade 3 or more non hematologic side effect with exception of:
  - Grade 3 nausea without symptomatic treatment,
  - Grade 3 diarrhea without symptomatic treatment,
  - Grade 3 asymptomatic elevations of liver enzymes (ASAT, ALAT, ALP) reversible within 7 days for patients without Liver involvement, or grade 4 for subjects with liver disease

⇒ Recommended dose 600 mg/d

Mourey et al. ESMO 2018

Immunotherapy in geriatric cancer patients

Immune checkpoint inhibitors have become one of the most successful immunotherapy strategies for various cancers [1]



- Another treatment generating excitement is chimeric antigen receptor (CAR) T-cell therapy, which uses adoptive cell therapy to improve the adaptive immune response.

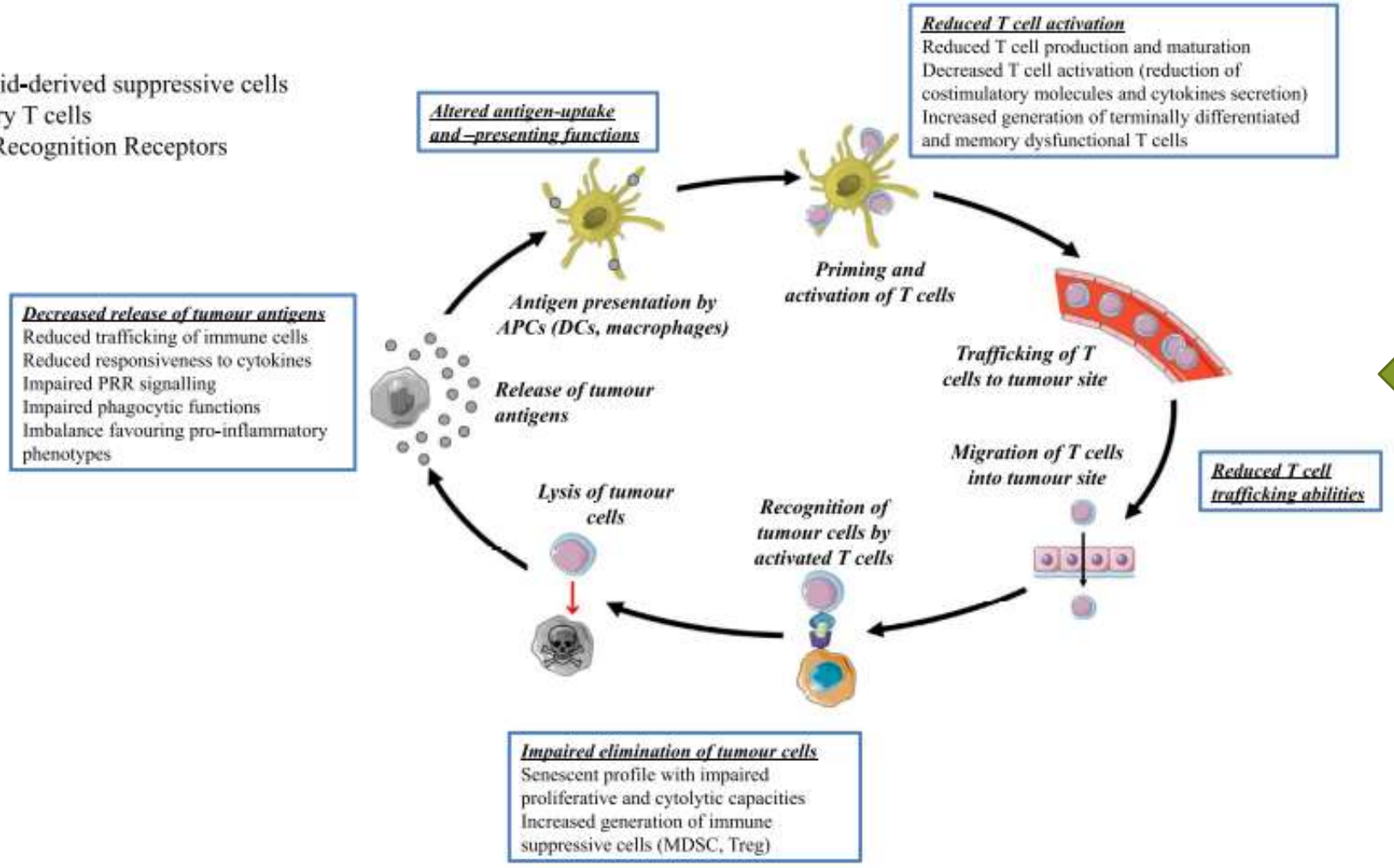
Problems with immunotherapy

- Increasing burden of cormorbidities
- Immunosenescence and dysregulation
- Very less representation in the clinical trials
- Metal health and social support networks
- Metabolic changes
- Overall functional status and frailty

Effects of immunotherapy in older adults

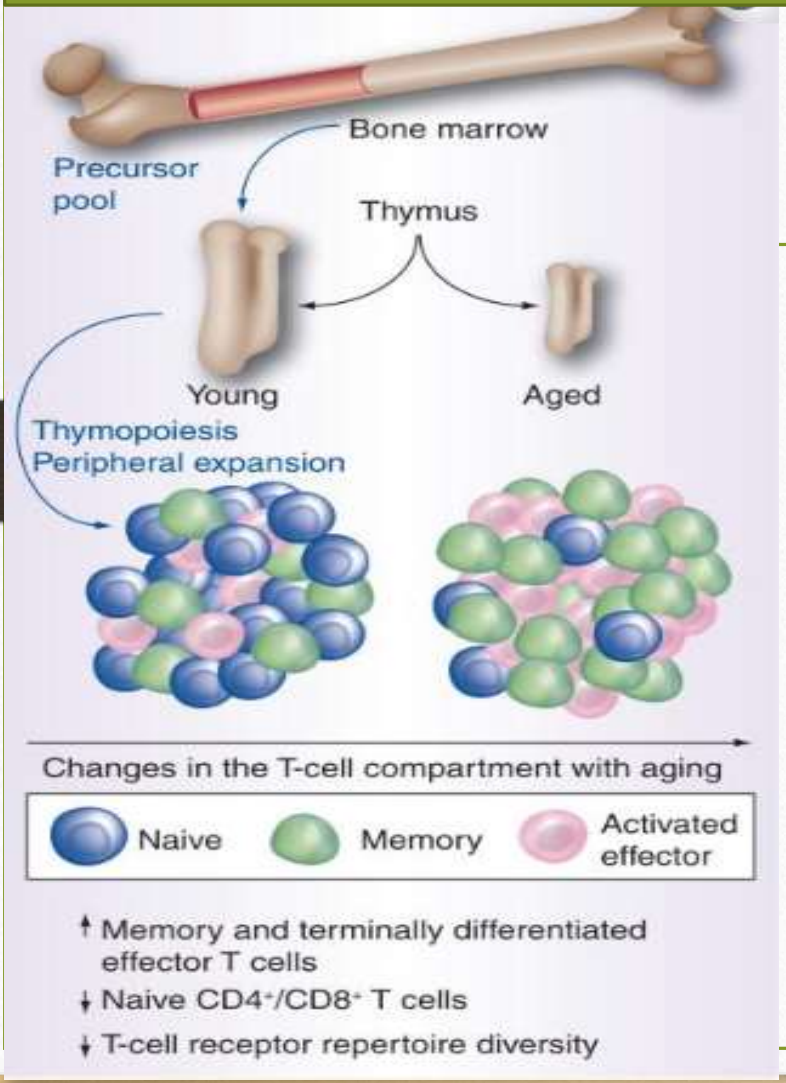
The effects of the aging immune system (immunosenescence) confer immune dysregulation and have both cellular and humoral aspects

MDSC: myeloid-derived suppressive cells
Treg: regulatory T cells
PRR: Pattern Recognition Receptors



Immunosenescence could impair each step of the anti-tumour immune response.

Age-associated changes characteristic of immunosenescence occur in T-cell populations



The young thymus supports more robust thymopoiesis with naive cells, which have the greatest T-cell receptor repertoire diversity and comprise the largest proportion of T cells.

With aging, thymus involution occurs and there is progressive loss of T-cell receptor repertoire diversity with the decreased population of naive T cells and there is an enlarged memory component that secretes most type 1 and 2 cytokines.

With repeated stimulation, the memory cells give rise to activated effector T cells, which are oligoclonal and have the most restricted T-cell receptor repertoire.

Result of immunosenescence and inflammation on immunotherapy

Dysfunctional immune response and chronic antigenic exposure = immunosenescence

↓

Low grade inflammation = inflamm-aging

↓

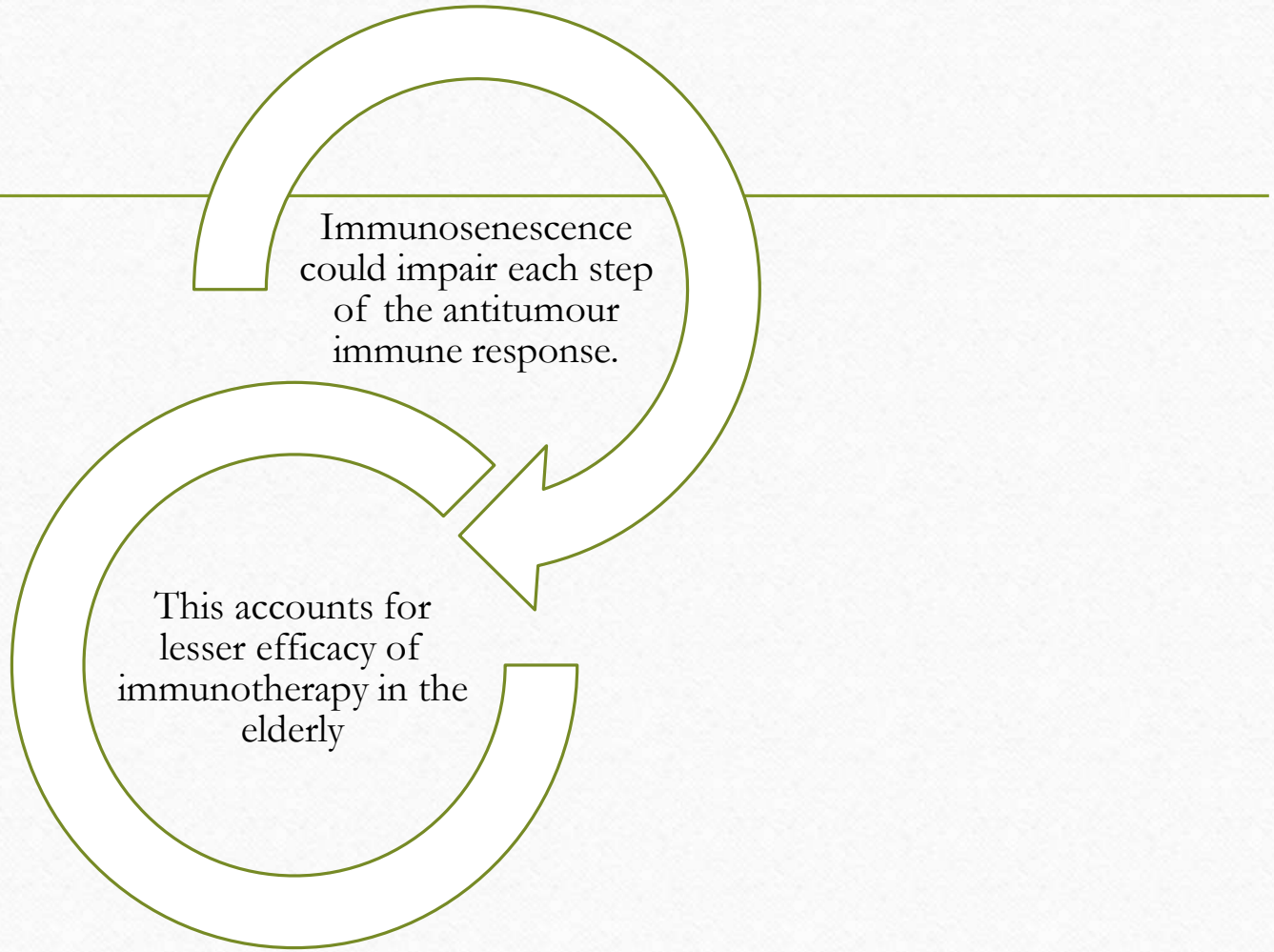
Tissue and cell damages

↓

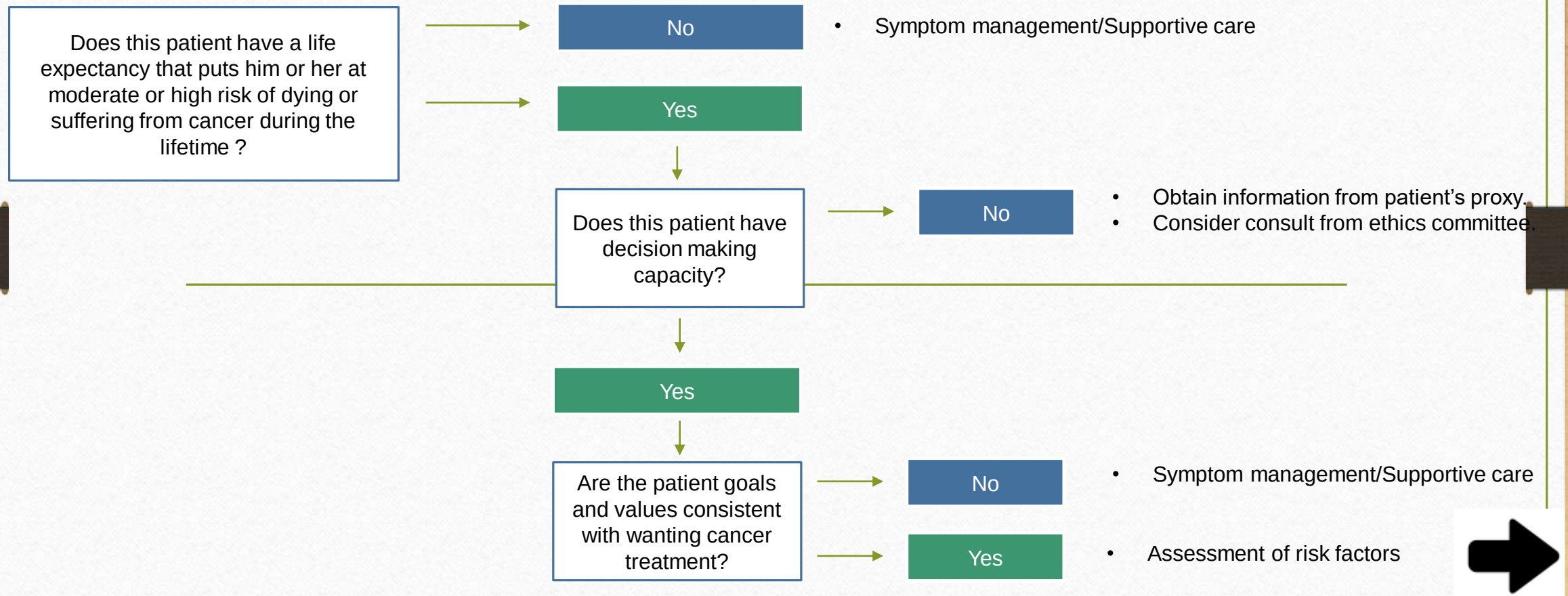
Immunosurvey escape

↓

Tumor development

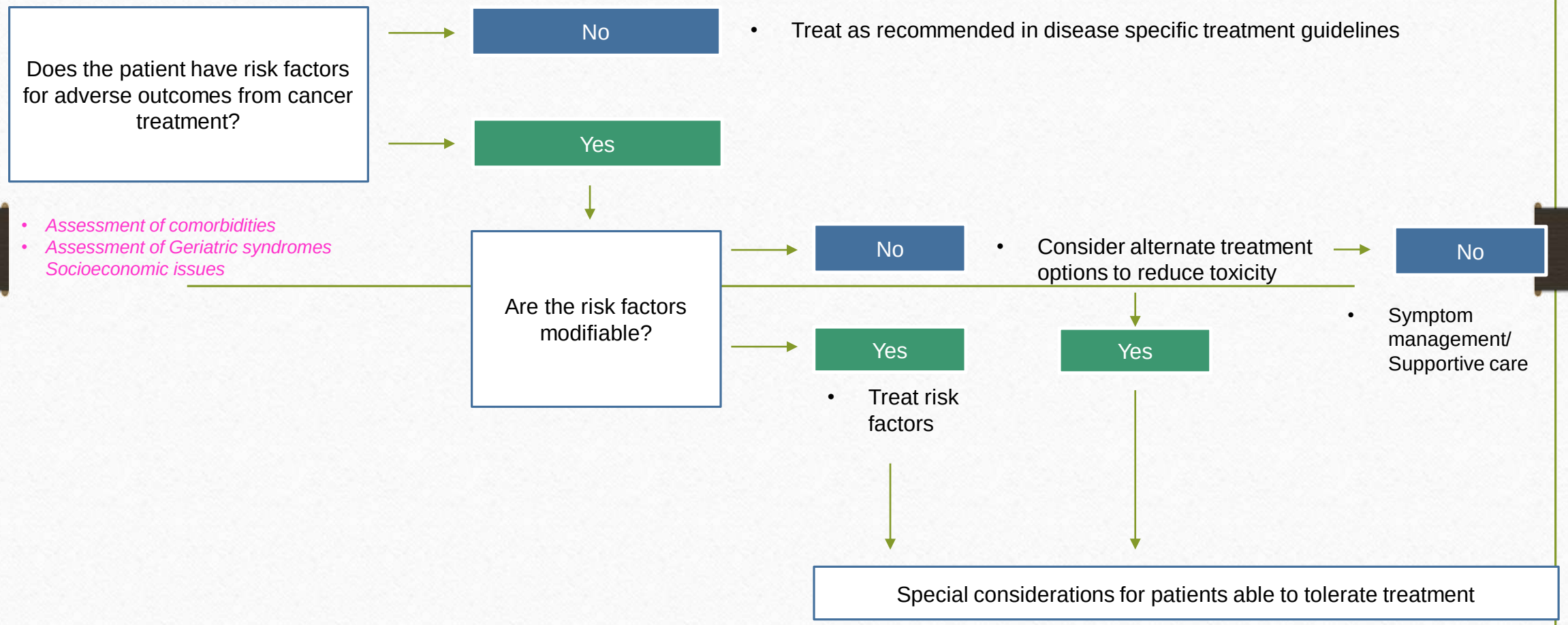


Approach to decision making based on GA



1. Hurria A. Senior Adult Oncology: Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2012 February ; 10(2): 162–209.

Approach to decision making based on GA



1. Hurria A. Senior Adult Oncology: Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2012 February ; 10(2): 162–209.

Conclusion

- Older adults are at an increased risk of cancer. Some of them cannot tolerate cancer medication.
- Fear of toxicity and unexpected side effects limit the use of standard chemotherapy.
- In patients ≥ 65 years receiving chemotherapy, geriatric assessment (GA) should be used to identify vulnerabilities that are not routinely captured in oncology assessments.
- Evidence supports, at a minimum, assessment of function, comorbidity, falls, depression, cognition, and nutrition.
- Well-designed prospective observational studies have found that items included in a GA can identify older patients at greatest risk for chemotherapy toxicity and mortality.
- GA-based tools are available that provide specific estimates for chemotherapy toxicity (CARG and CRASH) and can help to identify those patients at highest risk for early mortality (G8 and VES-13).

Thank You