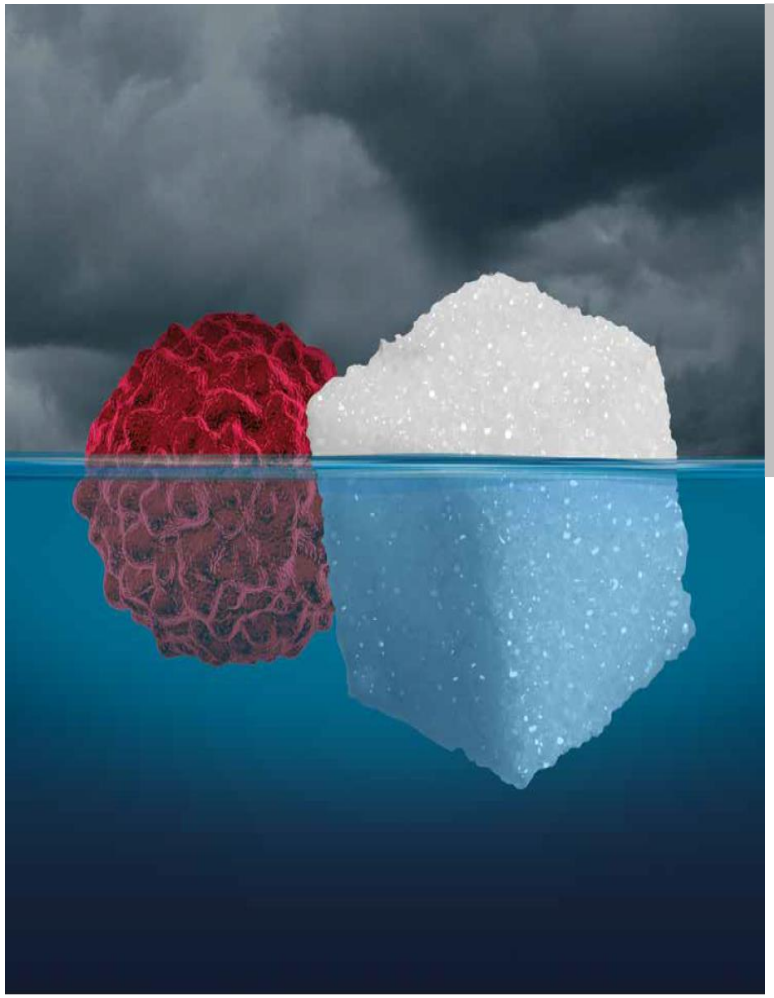


Complicanze glicometaboliche nella gestione del paziente oncologico

Tiziana Falbo
Oncologia Medica
I.N.I. - Grottaferrata (RM)

DIABETE E TUMORI NELLA PRATICA CLINICA:
RILEVANZA, CRITICITÀ, SOLUZIONI

ROMA, 9 Novembre 2019

UNAHOTELS DECÒ
Via Giovanni Amendola, 57

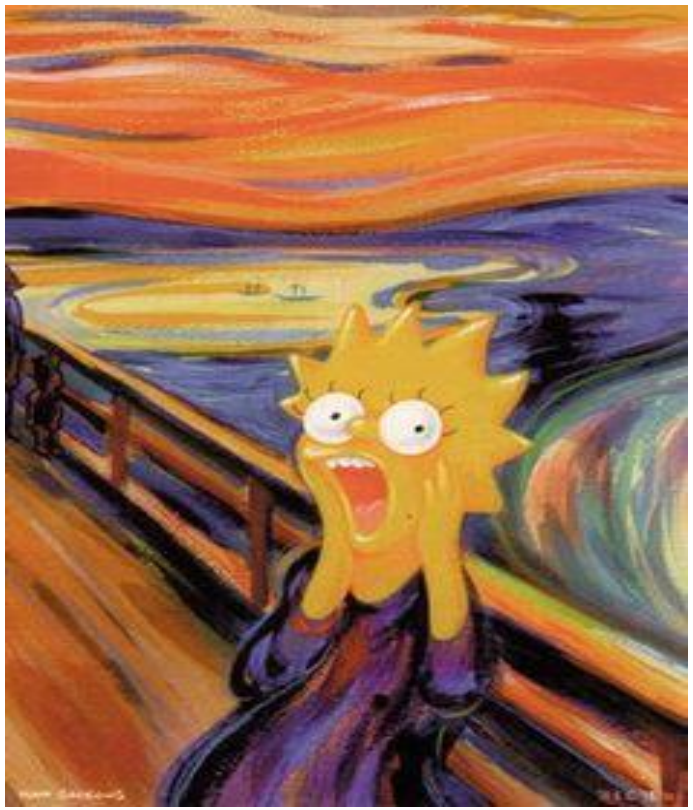
Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☒ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

☐ Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	**Company/Organization**



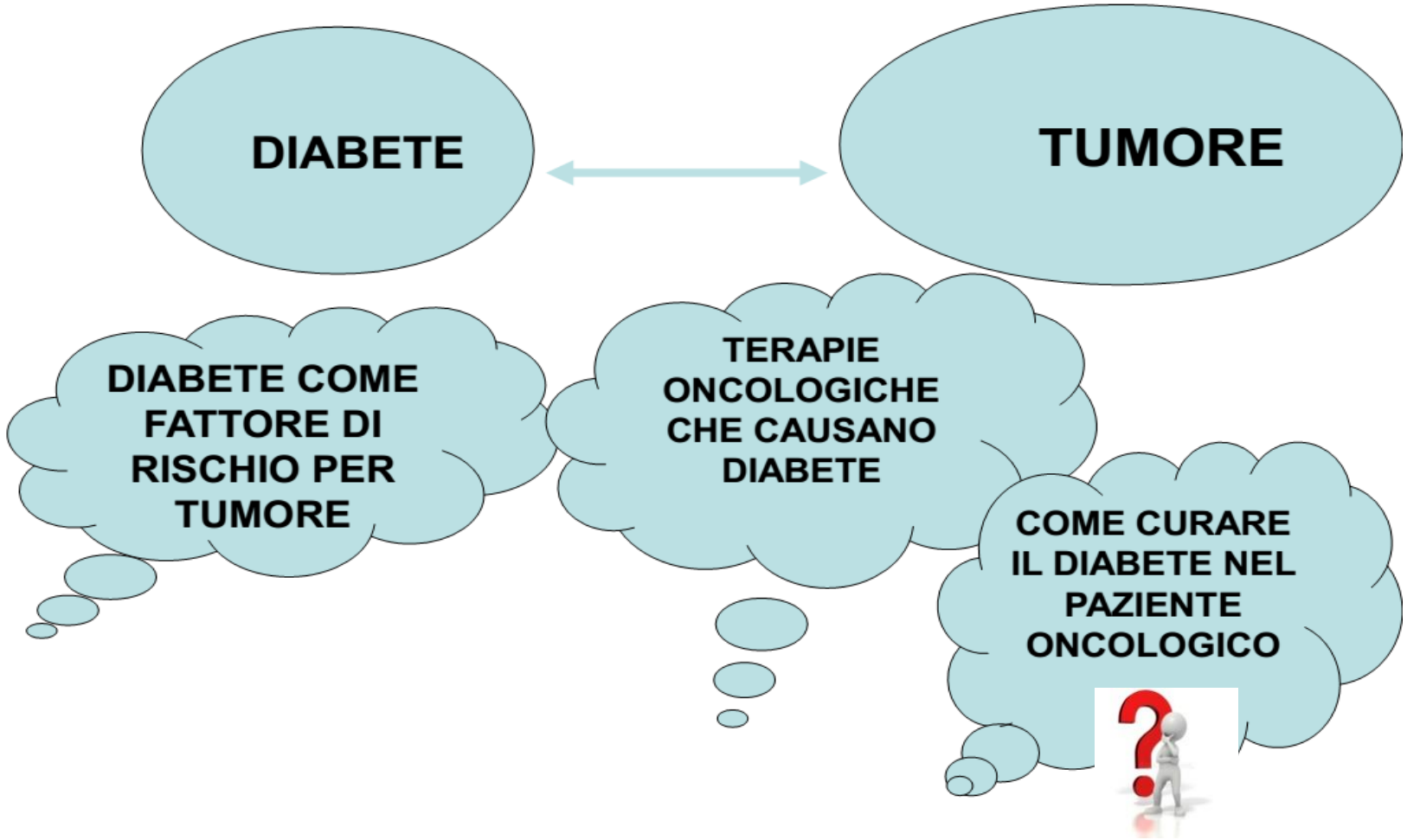
Paziente diabetico che sviluppa una neoplasia

Paziente che sviluppa diabete dopo chirurgia per neoplasia

Paziente che sviluppa diabete a seguito di terapie mediche per tumore

Paziente che sviluppa diabete a seguito di terapie di supporto a cure mediche per tumore

Due condizioni patologiche strettamente connesse….



Diabete e tumori…qualche premessa..

- Quando si parla di associazione Cancro – Diabete negli studi si fa per la maggior parte dei casi riferimento al DIABETE TIPO II (90% dei pz)

- Aumento del rischio di insorgenza di neoplasia nei soggetti diabetici per il tumore della mammella, il tumore dell'endometrio e HCC

- Il rischio di mortalità da neoplasia in soggetti con pre-esistente terapia diabetica aumenta

- Il diabete è protettivo nei confronti del tumore prostatico (bassi livelli di testosterone negli insulino-resistenti e polimorfisimi del gene HNF1B)

Vigneri P et al. Endocr Realt Cancer 2009

Yeap BB et al. Eur J Endocrinol 2009

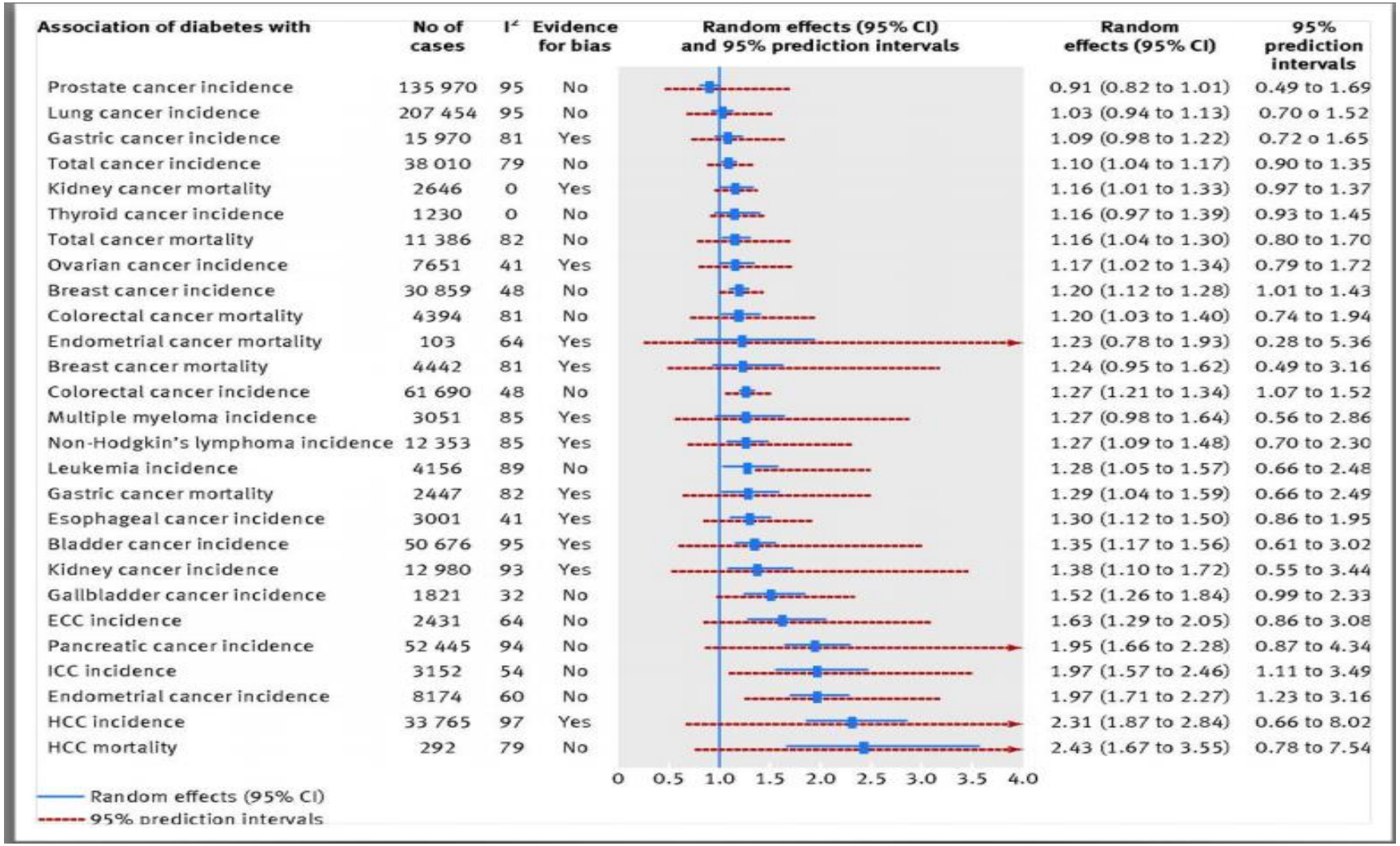
Lipscombe et al. Breast Cancer Res Treat 2008

Barone BB et al. JAMA 2008

Dimensione del problema

Diabetes and Risk of Cancer
Habib SL et al. ISRN Oncology 2013: 583786
GLOBOCAN 2012 (IARC)

Type 2 diabetes and cancer: Umbrella review of metanalyses of observational studies

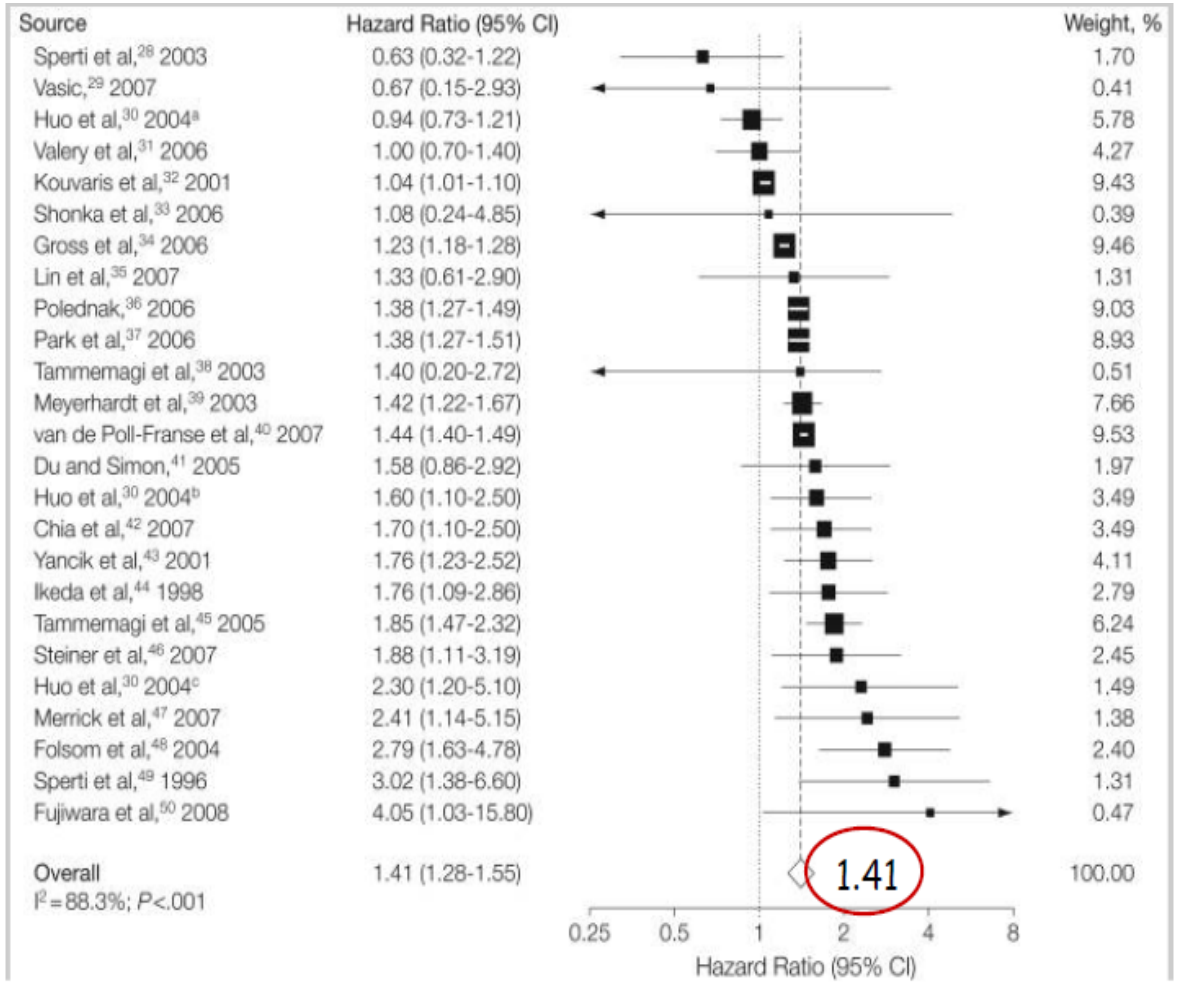


Tsilidis et al. BMJ 2015

Long-term All-Cause Mortality in Cancer Patients With Preexisting Diabetes Mellitus:

A Systematic Review and Meta-analysis

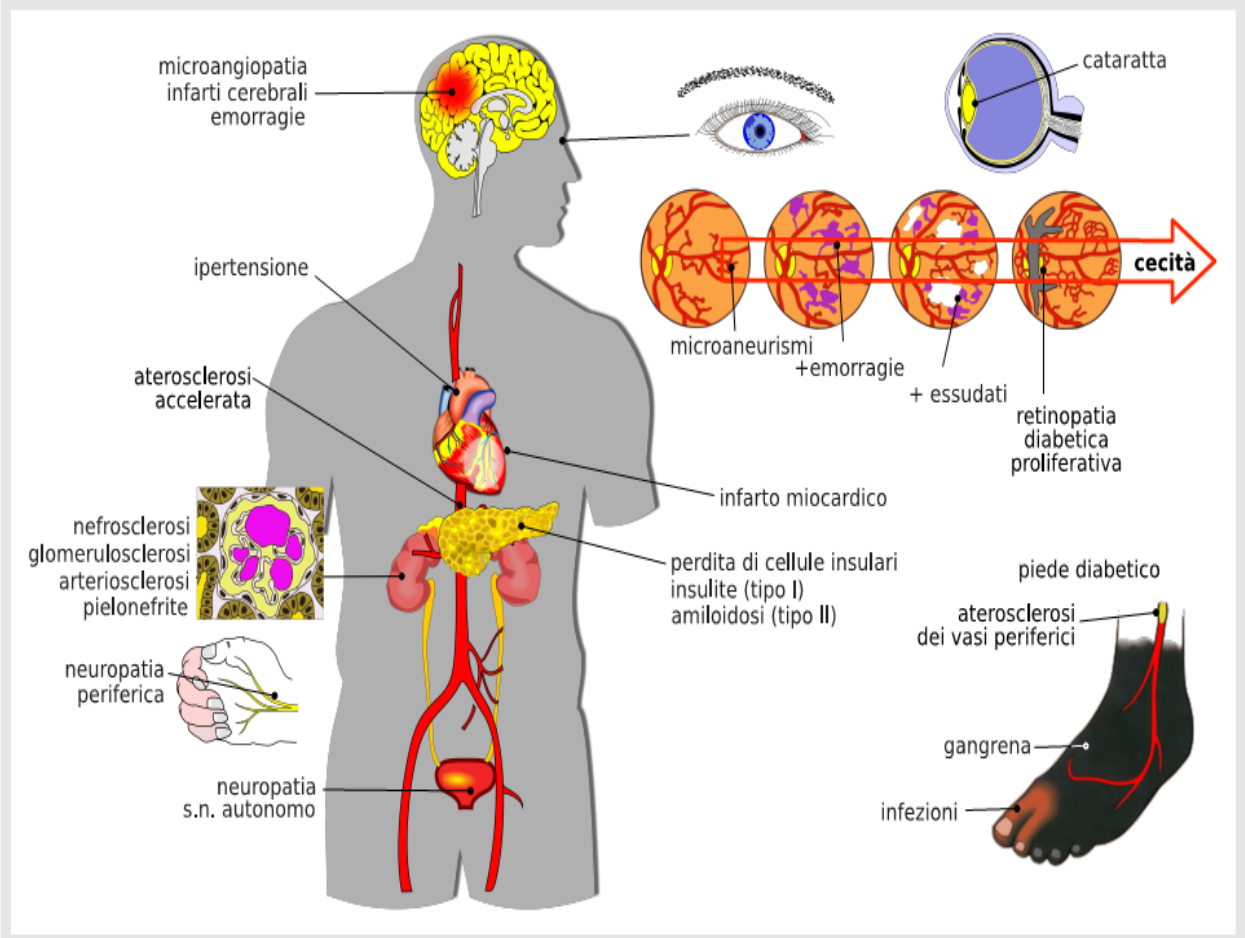
Bethany B. Barone, ScM, Hsin-Chieh Yeh, PhD, Claire F. Snyder, PhD, Kimberly S. Peairs,



I pazienti oncologici con preesistente diabete hanno un rischio maggiore di morte per tutte le cause rispetto a quelli senza diabete HR= 1.41

JAMA. 2008 December 17; 300(23): 2754–2764.

Complicanze secondarie del diabete



COMPLICANZE METABOLICHE ACUTE

- Ipoglicemia
- Chetoacidosi diabetica
- Iperglicemia iperosmolare non chetoacidosica

COMPLICANZE CRONICHE

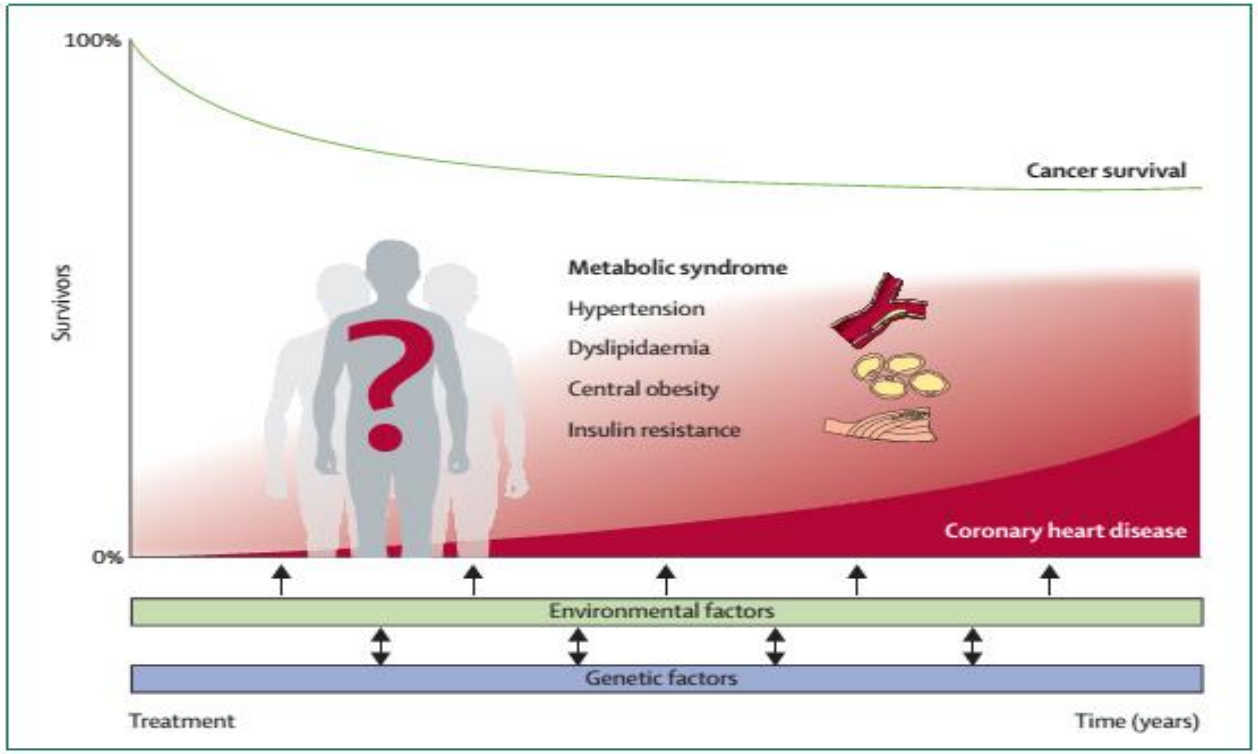
- Microvascolari
- Retinopatia
- Nefropatia
- Macroavascolari
- Cardiopatia ischemica
- Vasculopatia cerbrale
- Arteriopatia obliterante periferica
- Neurologiche
- Neuropatia periferica sensitivo-motoria
- Neuropatia autonomica
- Piede diabetico

The metabolic syndrome in cancer survivors

Lancet Oncol 2010; 11: 193–203

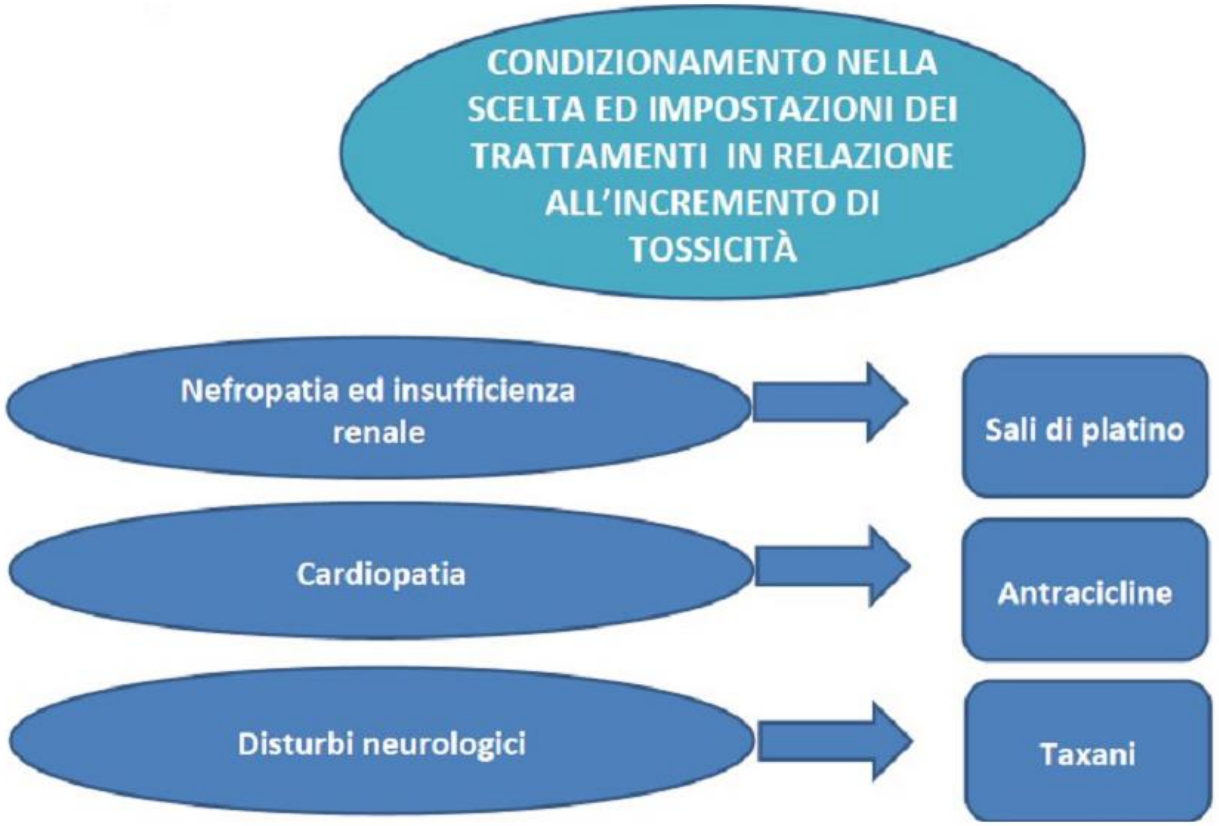
Esther C de Haas, Sjoukje F Oosting, Joop D Lefrandt, Bruce H R Wolffenbuttel, Dirk Th Sleijfer, Jourik A Gietema

The metabolic syndrome, as a cluster of cardiovascular risk factors, may represent an important connection between cancer treatment and its common late effect of cardiovascular disease. Insight into the aetiology of the metabolic syndrome after cancer treatment might help to identify and treat cancer survivors with increased cardiovascular risk. In this review, we summarise current knowledge on the prevalence and pathophysiology of the metabolic syndrome in cancer survivors, and discuss current intervention strategies with an emphasis on new developments.



La sindrome metabolica (sindrome-X, sindrome da resistenza all'insulina) consiste di una costellazione di anormalità metaboliche che conferiscono aumentato rischio di malattia cardiovascolare e diabete mellito

Come le complicanze da diabete influenzano le scelte farmacologiche dell'oncologo



- La decisione clinica è influenzata dalla presenza del diabete mellito
- Il diabete mellito impatta sulla sopravvivenza da chemioterapia
- I farmaci usati in oncologia possono causare diabete

J Clin Oncol 27:2170-2176. © 2009

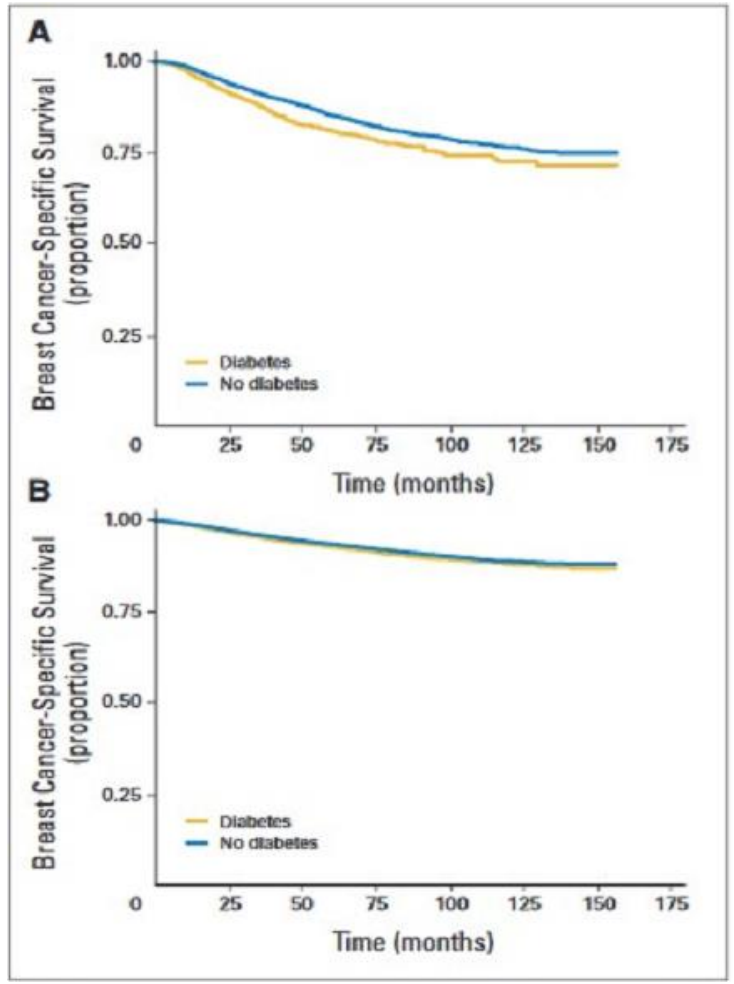
VOLUME 27 · NUMBER 13 · MAY 1 2009

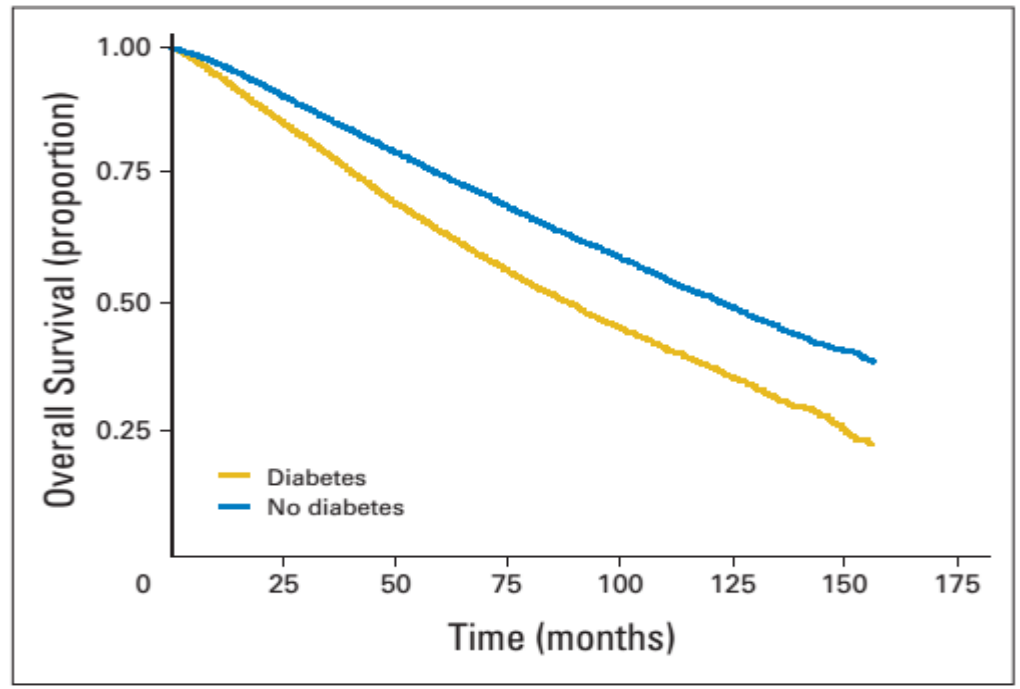
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Diabetes Mellitus on Complications and Outcomes of Adjuvant Chemotherapy in Older Patients With Breast Cancer

Tomasz P. Srokowski, Shenying Fang, Gabriel N. Hortobagyi, and Sharon H. Giordano





Conclusion

In this observational, hypothesis-generating study, patients who have breast cancer and diabetes are at increased risk of chemotherapy-related toxicities compared with nondiabetic patients who are receiving chemotherapy and have higher all-cause mortality.

Diabete e tumori

✓ **La presenza di diabete influisce sulla strategia terapeutica**:

- Alterazione della funzionalità renale
- Aumentato rischio di eventi vascolari
- Aumentato rischio di cardiotossicità
- Aumentato rischio di neuropatia

✓ **Il diabete condiziona la scelta dei trattamenti e delle terapie di supporto:**

- Utilizzo degli steroidi
- Antiemesi
- Farmaci che provocano iperglicemia

✓ **Nutrizione**

- Quale optimum di livello glicemico....

Clinical Challenges in Caring for Patients With Diabetes and Cancer

Diabetes Spectrum Volume 19, Number 3, 2006

Helen M. Psarakis, RN, APRN

Diabetes and cancer are two diagnoses that individually overwhelm both patients and clinicians. Approximately 8–18% of people with cancer have diabetes. Together, these two diseases can pose formidable challenges to clinicians caring for this difficult patient population. Unfortunately, our knowledge of this topic is limited by insufficient evidence to determine how best to manage diabetes while simultaneously treating cancer. This article seeks to review some of the most common problems encountered by clinicians caring for these patients.

Conclusion

Overall, the treatment of and therapies for diabetes in the setting of cancer present a major challenge for clinicians. Maintaining adequate glucose control reduces the incidence of infection in at-risk patients with cancer. Sustaining adequate nutrition and providing appropriate calories for patients receiving chemotherapy demands careful glucose control with whatever therapy improves the clinical situation. Having an understanding of the complexities of both diseases is necessary to achieve the best outcome.

L'Endocrinologo (2018) 19:185–190
https://doi.org/10.1007/s40619-018-0455-y

RASSEGNA

Gestione del diabete nel paziente oncologico

Marco Gallo[1] · Sara Belcastro[2]

Effetti avversi sul metabolismo glucidico, lipidico e pressorio di alcuni farmaci antitumorali

Categoria	Indicazioni principali	Glicemia	Lipidi	PAO	Sistema cardiovascolare
Chemioterapici tradizionali					
Antracicline (*doxorubicina, daunorubicina, epirubicina, idarubicina*)	Ca mammella, endometrio, ovaio, testicoli, polmoni, tiroide, sarcomi, linfomi, mieloma				↑ insufficienza cardiaca
Derivati del platino (*cisplatino, carboplatino, oxaliplatino*)	Ca polmone, stomaco e tratto digerente, tiroide, neoplasie tratto testa-collo e genitourinario	↑			
Antimetaboliti (*5-Fluorouracile*)	Ca colon-retto, pancreas	↑			
Alchilanti (*estramustina*)	Ca prostata	↑			
Taxani (*docetaxel, paclitaxel*)	Ca mammella, polmone, stomaco e tratto digerente, tiroide, neoplasie tratto testa-collo e genitourinario	↑			
L-asparaginasi	Leucemia linfocitica acuta	↑	↑ trigliceridi		
Diazossido	Insulinoma	↑			
Triossido d'arsenico	Leucemia acuta promielocitica	↑			
Bexarotene	linfoma cutaneo a cellule T, micosi fungoide		↑ trigliceridi		
Mitotane	Ca surrene		↑ colesterolo		
Steroidi	Linfomi, leucemie	↑		↑	
GnRH analoghi e inibitori sintesi androgenica	Ca prostata, mammella	↑	↑ colesterolo e trigliceridi	↑	↑ rischio eventi cardiovascolari
Inibitori dell'aromatasi (*letrozolo*)	Ca mammella		↑ colesterolo		↑ rischio eventi cardiovascolari
Progestinici (*megestrolo, medrossiprogesterone*)	Ca mammella, endometrio	↑	↑ colesterolo e trigliceridi	↑	
Terapie biologiche e radiofarmaci					
Analoghi somatostatina	Tumori neuroendocrini	↑			
Interferone alfa	Tumori neuroendocrini	↑			
Immunomodulanti e inibitori dell'angiogenesi					
Talidomide, lenalidomide	Mieloma multiplo	↑			
Target therapy					
Inibitori tirosin-kinasi: nilotinib, pazopanib e ponatinib	Leucemia mieloide cronica	↑			
sunitinib, ponatinib, lenvatinib, vandetanib	Ca fegato, rene, tiroide, leucemia mieloide cronica			↑	
Anticorpi monoclonali: bevacizumab, trastuzumab, lapatinib, Ibrutumab tioxetano	Ca colon-retto, polmone, rene, mammella, linfoma non Hodgkin follicolare	↑			↑ insufficienza cardiaca
Inibitori di mTOR: everolimus, temsirolimus	Tumori neuroendocrini, Ca mammella, rene, linfoma a cellule mantellari	↑	↑ colesterolo e trigliceridi		
Inibitori dei checkpoint immunologici: atezolizumab, avelumab, ipilimumab, nivolumab e pembrolizumab	Ca polmone, rene, melanoma	↑			
IGF-1 inibitori	Sarcomi, GIST, Ca polmone, surrene	↑			
Inibitori dell'istone deacetilasi: panobinostat, vorinostat	Mieloma multiplo	↑	↑ colesterolo		

Adverse glycaemic effects of cancer therapy: indications for a rational approach to cancer patients with diabetes

Marco Gallo[a,*], *Giovanna Muscogiuri*[b], *Francesco Felicetti*[c], *Antongiulio Faggiano*[d], *Francesco Trimarchi*[e], *Emanuela Arvat*[a], *Riccardo Vigneri*[f], *Annamaria Colao*[g]

Available online at www.sciencedirect.com
Metabolism
www.metabolismjournal.com

Agents interfering with insulin production/secretion	Agents reducing the insulin sensitivity
L-Asparaginase	Glucocorticoids
Diazoxide	Megestrol acetate
Immune checkpoint inhibitors	Targeted therapies
a) cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	a) Tyrosine-kinase inhibitors
- ipilimumab	- IR/IGF1R inhibitors
b) Anti-programmed cell death receptor-1 (PD-1) antibodies	- PI3K/AKT inhibitors
- nivolumab	b) mTOR inhibitors (everolimus)
- pembrolizumab	
c) Anti-programmed cell death ligand-1 (PD-L1) antibodies	
- atezolizumab	
- avelumab	

Diabete da corticosteroidi nel paziente oncologico

Il diabete steroideo si manifesta in circa il 20% dei casi (range 10-60%)

1% della popolazione generale assume steroidi *(Fardet L, Drug 2014)*

- **TIPO** di molecola (a breve-intermedia o lunga durata d'azione)
- **DOSE** (alte o basse dosi)
- SCHEMA di terapia (una volta/die o più somministrazioni/die)
- **DURATA**

Terapia antitumorale
Linfomi non-Hodgkin
Leucemie linfatiche acute e croniche
Terapia sintomatica
Controllo dolore, nausea, vomito, anoressia, iperter-mia, fatigue
Controllo reazioni allergiche (estemporaneamente o negli schemi chemioterapici)
Come antiedemigeni in presenza di metastasi ence-faliche o del SNC
Controllo della dispnea da ostruzione delle vie aeree, della linfangite o della sindrome cavale

CHI SVILUPPERÀ DIABETE in corso di terapia con steroidi?

Tipo di STEROIDE

Fattori di rischio

- Familiarità per DM
- Obesità, sindrome metabolica
- PCOS
- Pregresso diabete gestazionale
- Pregresso diabete steroideo

- **Età**
- **Malattia concomitante (es. AR)**

➢**Pre-diabete (IFG, IGT)**

Tipo di **PAZIENTE**

2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients

Annals of Oncology 27 (Supplement 5): v119–v133, 2016
doi:10.1093/annonc/mdw270

F. Roila[1], A. Molassiotis[2], J. Herrstedt[3], M. Aapro[4], R. J. Gralla[5], E. Bruera[6], R. A. Clark-Snow[7],

Table 3. Recommended doses of corticosteroids[a] (dexamethasone)

Dexamethasone	Dose and schedule
High risk	
Acute emesis	20 mg once [12 mg when used with (fos) aprepitant or netupitant][b]
Delayed emesis	8 mg bid for 3–4 days [8 mg once daily when used with (fos)aprepitant or netupitant]
Moderate risk	
Acute emesis	8 mg once
Delayed emesis	8 mg daily for 2–3 days (many panellists give the dose as 4 mg bid)
Low risk	
Acute Emesis	4–8 mg once

[a]While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.
[b]The 12 mg dose of dexamethasone is the only one tested with (fos) aprepitant/netupitant in large, randomised trials.

IN OGNI CASO SOLO IN ASSENZA DI EMESI E' LECITO RIDURRE I DOSAGGI DEI CORTICOSTEROIDI

Table 1. Emetogenic potential of single intravenous antineoplastic agents

	IV chemotherapy		Oral chemotherapy[a]
High	Anthracycline/cyclophosphamide combination[b]		Hexamethylmelamine
	Carmustine		Procarbazine
	Cisplatin		
	Cyclophosphamide ≥1500 mg/m^2		
	Dacarbazine		
	Mechlorethamine		
	Streptozocin		
Moderate	Alemtuzumab	Epirubicin	Bosutinib
	Azacitidine	Idarubicin	Ceritinib
	Bendamustine	Ifosfamide	Crizotinib
	Carboplatin	Irinotecan	Cyclophosphamide
	Clofarabine	Oxaliplatin	Imatinib
	Cyclophosphamide <1500 mg/m^2	Romidepsin	Temozolomide
	Cytarabine >1000 mg/m^2	Temozolomide[c]	Vinorelbine
	Daunorubicin	Thiotepa[d]	
	Doxorubicin	Trabectedin	
Low	Aflibercept	Ipilimumab	Afatinib
	Belinostat	Ixabepilone	Axatinib
	Blinatumomab	Methotrexate	Capecitabine
	Bortezomib	Mitomycin	Dabrafenib
	Brentuximab	Mitoxantrone	Dasatinib
	Cabazitaxel	Nab-paclitaxel	Everolimus
	Carfilzomib	Paclitaxel	Etoposide
	Catumaxumab	Panitumumab	Fludarabine
	Cetuximab	Pemetrexed	Ibrutinib
	Cytarabine ≤1000 mg/m^2	Pegylated liposomal doxorubicin	Idelalisib
	Docetaxel	Pertuzumab	Lapatinib
	Eribulin	Temsirolimus	Lenalidomide
	Etoposide	Topotecan	Olaparib
	5-Fluorouracil	Trastuzumab-emtansine	Nilotinib
	Gemcitabine	Vinflunine	Pazopanib
			Ponatinib
			Regorafenib
			Sunitinib
			Tegafur uracil
			Thalidomide
			Vandetanib
			Vorinostat
Minimal	Bevacizumab	Pembrolizumab	Chlorambucil
	Bleomycin	Pixantrone	Erlotinib
	Busulfan	Pralatrexate	Gefitinib
	2-Chlorodeoxyadenosine	Rituximab	Hydroxyurea
	Cladribine	Trastuzumab	Melphalan
	Fludarabine	Vinblastine	Methotrexate
	Nivolumab	Vincristine	L-phenylalanine mustard
	Ofatumumab	Vinorelbine	Pomalidomide
			Ruxolitinib
			Sorafenib
			6-Thioguanine
			Vemurafenib
			Vismodegib

Online Exclusive Article

Hyperglycemic-Inducing Neoadjuvant Agents Used in Treatment of Solid Tumors: A Review of the Literature

Oncology Nursing Forum • Vol. 41, No. 6, November 2014

Denise Soltow Hershey, PhD, FNP-BC, Ashley Leak Bryant, PhD, RN, OCN®,
Jill Olausson, RN, MSN, CDE, Ellen D. Davis, MS, RN, CDE, FAADE,
Veronica J. Brady, MSN, FNP-BC, BC-ADM, CDE, and Marilyn Hammer, PhD, DC, RN

Conclusions: Findings suggest patients are at risk for the development of hyperglycemia from certain chemotherapeutic agents. Docetaxel, everolimus, and temsirolimus alone or in combination with other agents can promote hyperglycemia. Androgen-deprivation therapy commonly used in prostate cancer, increases the risk for the development of hyperglycemia and diabetes.

Farmaci chemioterapici e diabete

- Il Diabete indotto dalle terapie oncologiche è stato in passato un argomento poco approfondito per la bassa incidenza dell'evento
- Nessun farmaco storico si dimostra chiaramente causale nei confronti dell'insorgenza del Diabete
- Sono maggiormente implicati i farmaci orali e dopo lungo periodo di assunzione di quanto non siano i farmaci endovena
- Gli inibitori di mTOR tra i nuovi farmaci risultano essere i più implicati

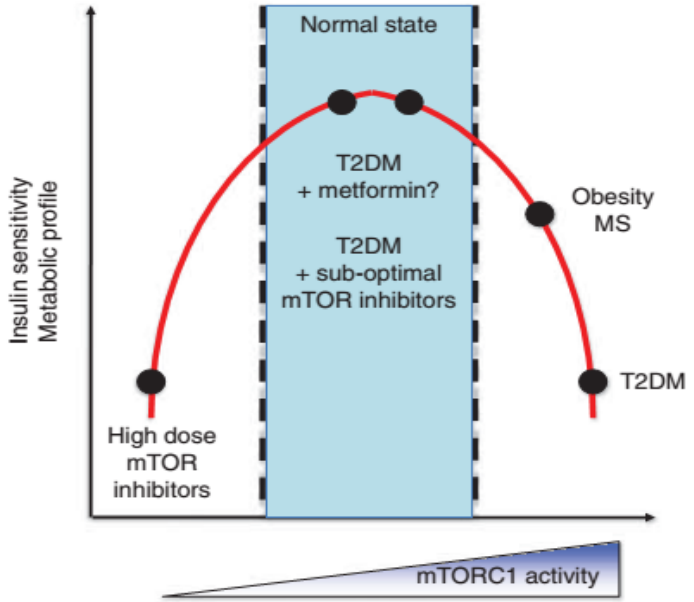
ENDOCRINE SIDE EFFECTS OF ANTI-CANCER DRUGS

Effects of anti-cancer targeted therapies on lipid and glucose metabolism

Review

Bruno Vergès, Thomas Walter[1] and Bertrand Cariou[2]

Drug	Types of cancer	*n*	Hyperglycemia (%)		Hypercholesterolemia (%)		Hypertriglyceridemia (%)	
			All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4
Everolimus								
Everolimus	Renal cell carcinoma	269	50	12	76	3	71	<1
Placebo (3)		135	23	1	32	0	30	0
Everolimus	Pancreatic NETs	204	13	5	ND	ND	ND	ND
Placebo (2)		203	4	2				
Everolimus+Oct	Gastrointestinal NETs	215	12	5	6	ND	ND	ND
Placebo+Oct (64)		211	2	0.5	1			
Everolimus	Breast	482	13	4	ND	ND	ND	ND
Placebo (4)		238	2	<1	ND	ND	ND	ND
Everolimus	Subendymal giant cell astrocytoma with TBS	78	ND	ND	ND	ND	ND	ND
Placebo (5)		39						
Temsirolimus								
Temsirolimus	Renal cell carcinoma	208	26	11	24	1	27	3
Interferon		200	11	2	4	0	14	1
Temsi+interferon (6)		208	17	6	26	2	38	8
Temsirolimus+letrozole	Breast cancer	550	13	4	12	1	11	2
Placebo+letrozole (53)		553	5	1	6	<0.5	5	<0.5
Temsirolimus	Mantle cell lymphoma	108	ND	ND	ND	ND	ND	ND
Investigator's choice (7)		53	ND	ND	ND	ND	ND	ND



Relationship between mTORC1 activity and metabolic homeostasis. The U-shaped curve indicates that too little or too much mTORC1 activity is associated with insulin resistance and altered metabolic profile.

European Journal of Endocrinology
(2014) **170**, R43–R55

ENDOCRINE SIDE EFFECTS OF ANTI-CANCER DRUGS

Effects of anti-cancer targeted therapies on lipid and glucose metabolism

Review

Bruno Vergès, Thomas Walter[1] and **Bertrand Cariou**[2]

Incidence of hyperglycemia and hypoglycemia induced by tyrosine kinase inhibitor (TKI) in phase III studies.

Drug	Types of cancer	*n*	Hyperglycemia (%)		Hypoglycemia (%)	
			All grades	Grades 3–4	All grades	Grades 3–4
Nilotinib						
Nilotinib	Chronic myeloid leukemia	556	38	5	ND	ND
Imatinib (14)		280	20	0	ND	ND
Nilotinib	Gastrointestinal stromal tumor	165	ND	ND	ND	ND
Control (84)		83	ND	ND	ND	ND
Pazopanib						
Pazopanib	Renal cell carcinoma	290	41	2	17	1
Placebo (12)		145	33	1	3	0
Pazopanib	Soft tissue sarcoma	239	ND	ND	ND	ND
Placebo (13)		123	ND	ND	ND	ND
Sunitinib						
Sunitinib	Renal cell carcinoma	375	15			
Interferon α (10)		360				
Sunitinib	Pancreatic NETs	83	ND	ND	ND	ND
Placebo (11)		82	ND	ND	ND	ND
Sunitinib	Gastrointestinal stromal tumor	202	ND	ND	ND	ND
Placebo (9)		102	ND	ND	ND	ND

	mTOR inhibitors	TKIs
Total cholesterol	↑	↔ (↓ in one study with imatinib)
Triglycerides	↑	↔ (↓ in one study with imatinib)
LDL cholesterol	↑	
HDL cholesterol	↔ or ↑	
Glycemia	↑	↑ or ↓

Conclusion

Targeted therapies are widely used in oncology for the treatment of a variety of malignancies. Considering the results from the phase III trials, it is obvious that some of these targeted therapies, especially mTOR inhibitors, are associated with an increased risk of metabolic complications. This risk should be anticipated by the identification of high-risk patients and managed by a close monitoring of metabolic parameters, in tight collaboration with physicians specialized in diabetes and endocrinology.

European Journal of Endocrinology
(2014) **170**, R43–R55

Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management

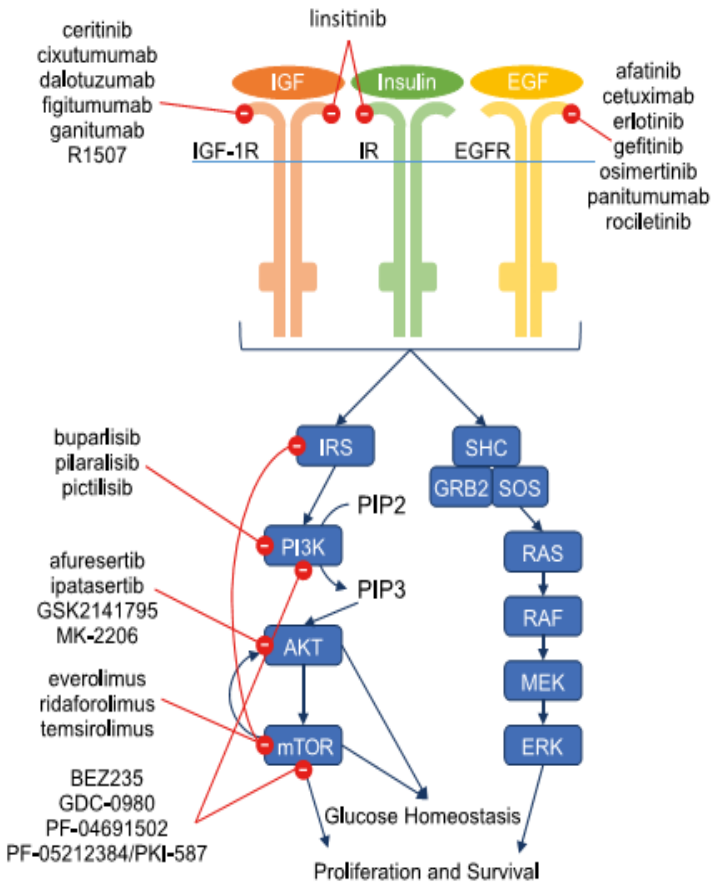
The Oncologist 2016;21:1326–1336

JONATHAN W. GOLDMAN,[a] MELODY A. MENDENHALL,[a] SARAH R. RETTINGER[b]

The Oncologist®

Cancer drugs with known side effect of hyperglycemia

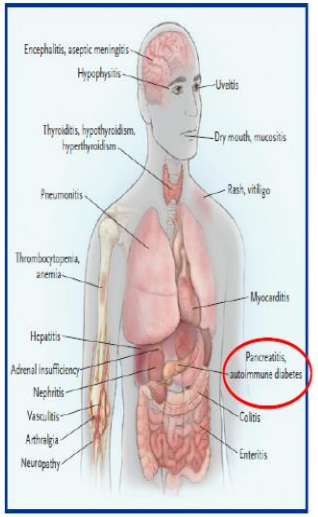
Targeted therapy type and pathway	Drug name	Hyperglycemia across studies: Range of any grade, %	Hyperglycemia across studies: Highest incidence of grade ≥3, %
Tyrosine kinase inhibitors			
IGF-1R	Cixutumumab [10–13]	17–100	46 [13]
	Dalotuzumab [14, 15]	19–100	32 [15]
	Figitumumab[a] [16–18]	64–100	22 [18]
	Ganitumab[a] [19]	10	NR
	R1507 [20, 21]	5–19	3 [21]
Dual IGF-1R/IR	Linsitinib [22–24]	3–37	5 [23]
Other inhibitors of IGF-1R	Ceritinib [25]	49	13
	Ganetespib [26–29]	0–64	25 [26]
EGFR	Gefitinib [30]	5	NR
	Panitumumab [31]	5	5
	Rociletinib [32]	46	25
PI3K, AKT, and mTOR inhibitors			
PI3K	Buparlisib [33]	31	8
	Pictilisib [34]	2	2[b]
	Pilaralisib [35]	7	0
AKT	Afuresertib[c] [36]	3	0
	GSK2141795[d] [37]	21	5
	Ipatasertib[d] [38]	9	0
	MK-2206[e] [39–41]	8–30	9 [40]
mTOR	Everolimus [42–54]	7–93	22 [53]
	Ridaforolimus [55–57]	11–29	19 [57]
	Temsirolimus [58–66]	7–76	24 [61]
Dual PI3K/mTOR	BEZ235 [67]	24	9
	GDC-0980 [68]	46	46
	PF-04691502 [69]	27	11
	PF-05212384/PKI-587 [70]	26	2
PD-1 inhibitors			
PD-1	Nivolumab [71]	<1	0
	Pembrolizumab [72]	40–48	3



Iperglicemia e nuovi farmaci : immunoterapia

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.[a]

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma



Pembrolizumab e nivolumab sono anticorpi mirati al recettore PD-1 (programmed death-1 receptor).

La loro azione sul sistema immunitario può comportare una distruzione autoimmune delle cellule β delle isole di Langerhans con conseguente insorgenza di iperglicemia e diabete mellito di tipo I.

In studi di fase I che hanno indagato il pembrolizumab in pazienti affetti da melanoma metastatico o tumore del polmone non a piccole cellule, l'incidenza di iperglicemia (qualsiasi grado) è stata del 40% e 48% rispettivamente (grado 3, 2%;grado 4, 3%).

In particolare il diabete mellito è stato riportato in 1 caso su 206 pazienti in un trial di fase III che ha testato il nivolumab nel trattamento del melanoma metastatico.

Tossicità rare < 10%

Distretto corporeo o organo	*Tossicità*
Tratto gastroenterico	Epatite Pancreatite
Sistema endocrino	SIADH Insufficienza surrenalica primitiva o centrale Diabete mellito

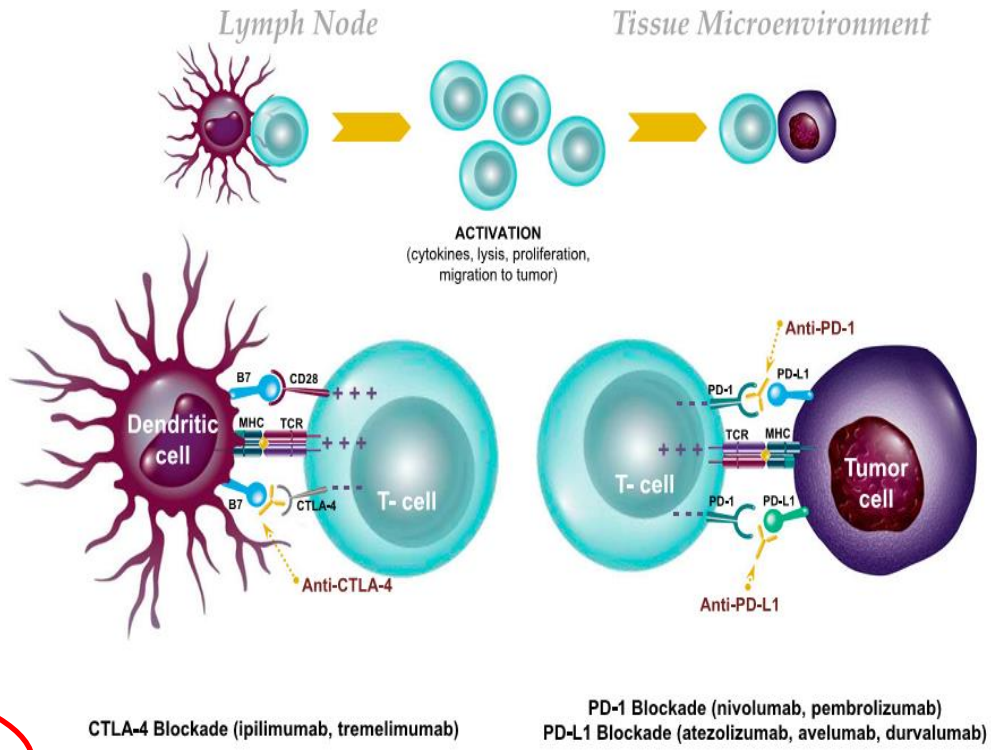
Goldman JW et al. The Oncologist 2016
Hofmann L et al. eur J Cancer 2016
Usui Y et al. J Thorac Oncol 2017

Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors

Diabetes Volume 67, August 2018

Angeliki M. Stamatouli,[1] Zoe Quandt,[2] Ana Luisa Perdigoto,[1] Pamela L. Clark,[3] Harriet Kluger,[4] Sarah A. Weiss,[4] Scott Gettinger,[4] Mario Sznol,[4] Arabella Young,[2] Robert Rushakoff,[2] James Lee,[5] Jeffrey A. Bluestone,[2,6] Mark Anderson,[2] and Kevan C. Herold[1,3]

Insulin-dependent diabetes may occur in patients with cancers who are treated with checkpoint inhibitors (CPIs). We reviewed cases occurring over a 6-year period at two academic institutions and identified 27 patients in whom this developed, or an incidence of 0.9%. The patients had a variety of solid-organ cancers, but all had received either anti–PD-1 or anti–PD-L1 antibodies. Diabetes presented with ketoacidosis in 59%, and 42% had evidence of pancreatitis in the peridiagnosis period. Forty percent had at least one positive autoantibody and 21% had two or more. There was a predominance of HLA-DR4, which was present in 76% of patients. Other immune adverse events were seen in 70%, and endocrine adverse events in 44%. We conclude that autoimmune, insulin-dependent diabetes occurs in close to 1% of patients treated with anti–PD-1 or –PD-L1 CPIs. This syndrome has similarities and differences compared with classic type 1 diabetes. The dominance of HLA-DR4 suggests an opportunity to identify those at highest risk of these complications and to discover insights into the mechanisms of this adverse event.

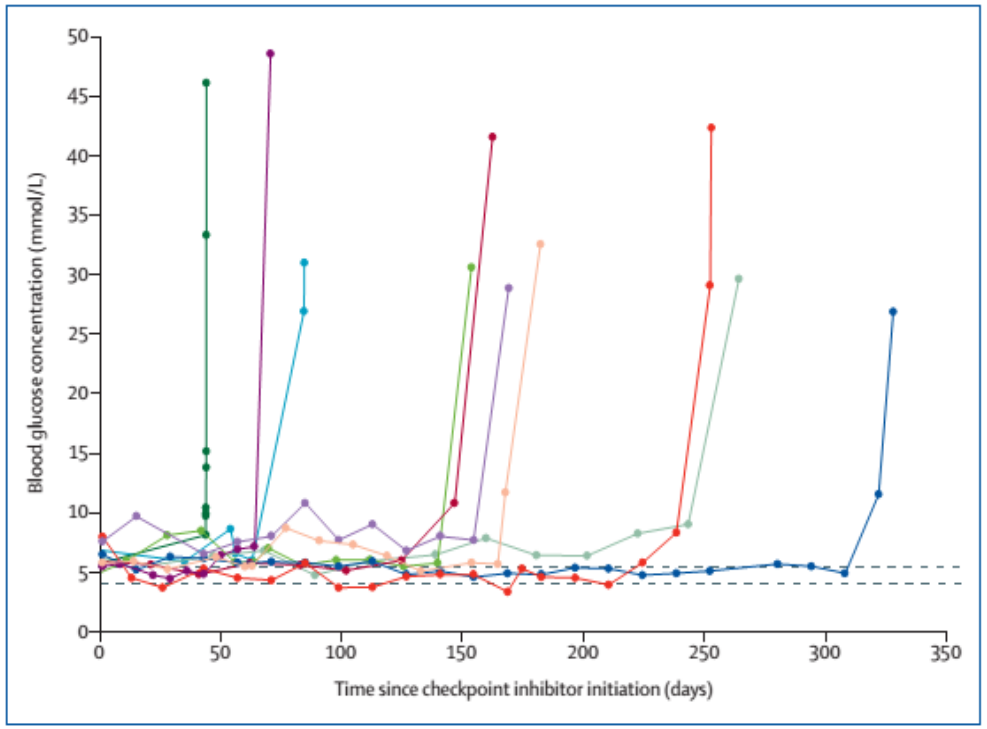


CTLA-4 Blockade (ipilimumab, tremelimumab)

PD-1 Blockade (nivolumab, pembrolizumab)
PD-L1 Blockade (atezolizumab, avelumab, durvalumab)

Checkpoint inhibitor-induced insulin-dependent diabetes: an emerging syndrome

Checkpoint inhibitor-induced diabetes has been reported in roughly 0·9% of patients treated with checkpoint inhibitors,[9] but with the increasing use of such treatments, the prevalence of checkpoint inhibitor-induced diabetes is also increasing.



Anti–PD-1 and Anti–PDL-1 Monoclonal Antibodies Causing Type 1 Diabetes

Mahnaz Mellati[1], Keith D. Eaton[2], Barbara M. Brooks-Worrell[1,3], William A. Hagopian[1,4], Renato Martins[2], Jerry P. Palmer[1,3] and Irl B. Hirsch[1]

Sept 2015: 38(39)

We conclude that anti–PD-1, and possibly anti–PDL-1, antibody use can result in a rapid progression of autoimmune diabetes in human subjects who have a high underlying **genetic predisposition** to type 1 diabetes, similar to what has been reported in a rodent model. Once diagnosed, autoimmune diabetes with severe insulin deficiency is a treatable disease, but the rapid presentation with DKA is important to recognize due to its morbidity and potential mortality. Physicians treating patients with this novel class of cancer therapy should be aware of this potential adverse event.

The NEW ENGLAND JOURNAL of MEDICINE

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

Michael A. Postow, M.D., Robert Sidlow, M.D., and Matthew D. Hellmann, M.D.

N Engl J Med 2018;378:158-68.
DOI: 10.1056/NEJMra1703481

Treatment with checkpoint inhibitors has been associated with acute onset of type 1 diabetes mellitus in approximately 0.2 percent of cases. As an example, in a series of five cases, patients presented with severe hyperglycemia or diabetic ketoacidosis; all required insulin therapy at diagnosis and remained insulin-dependent for diabetic control.

It is important to monitor glucose with each dose of immunotherapy

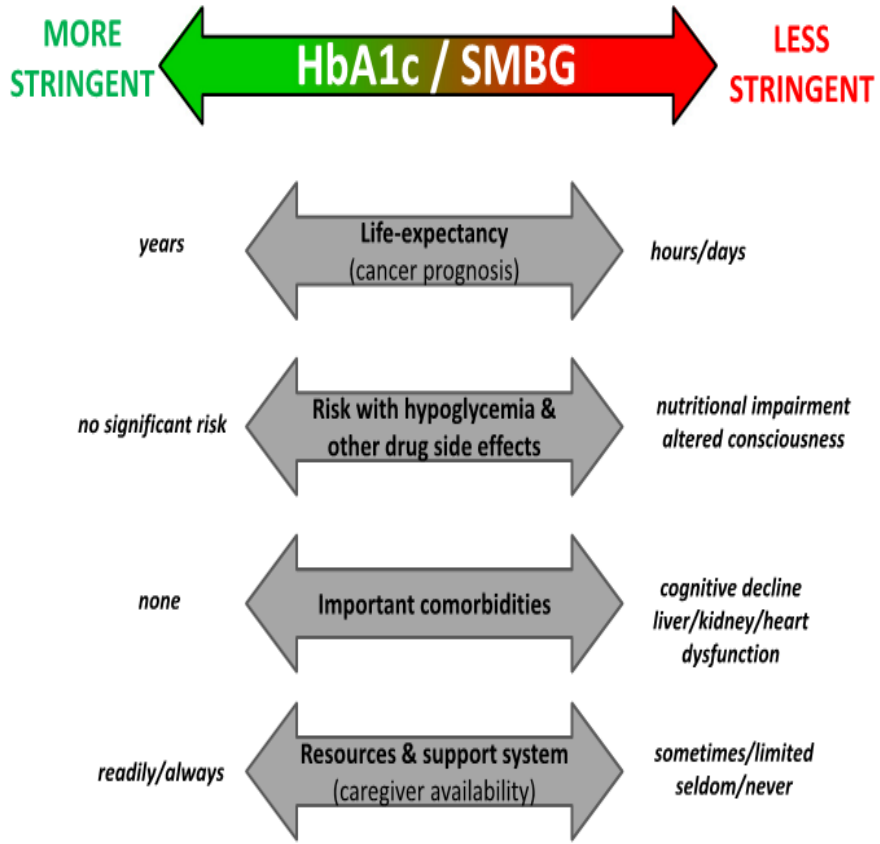
Adverse glycaemic effects of cancer therapy: indications for a rational approach to cancer patients with diabetes

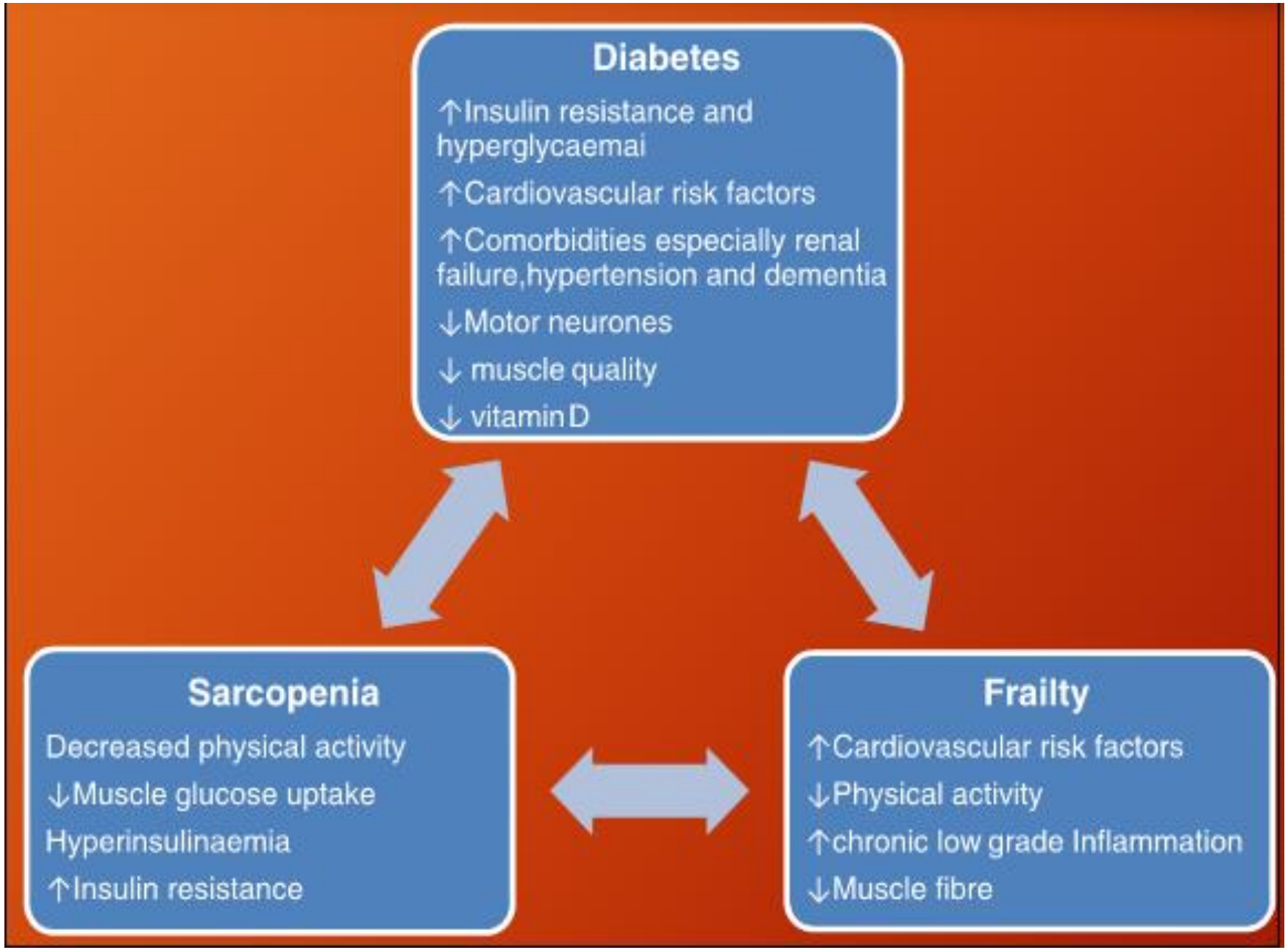
Marco Gallo[a,*], *Giovanna Muscogiuri*[b], *Francesco Felicetti*[c], *Antongiulio Faggiano*[d], *Francesco Trimarchi*[e], *Emanuela Arvat*[a], *Riccardo Vigneri*[f], *Annamaria Colao*[g]

Available online at www.sciencedirect.com

Metabolism

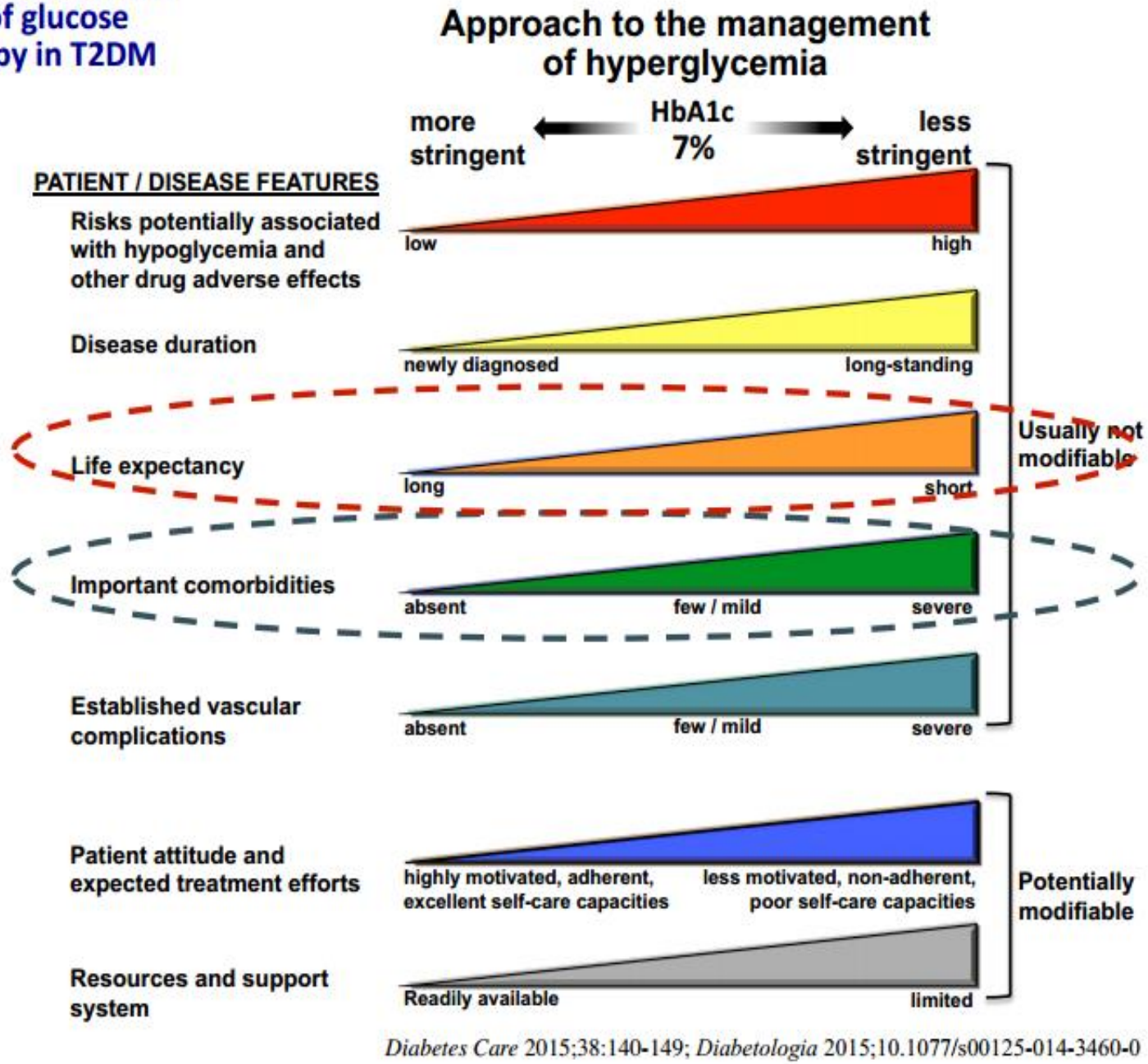
www.metabolismjournal.com





Sinclair A.J.2017

Modulation of the intensiveness of glucose lowering therapy in T2DM



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Anti hyperglycemic therapy

- L'obiettivo NON è la prevenzione delle complicanze a lungo termine, ma il supporto.
- E' necessario considerare:

– Aspettativa di vita

– Limitare ipo o iperglicemia severa

– Limitare i disagi aggiuntivi

(polidispsia, poliuria, disidratazione, malessere, sintomi neuroglucopenici)

- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - ***Individualization*** is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%$^{+}$) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

ADA-EASD Position Statement Update: Management of Hyperglycemia in T2DM, 2015

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

Insulina

- La terapia antidiabetica più appropriata è quella con insulina perché:

– Iperglicemia generalmente severa

– Scarsa flessibilità ed efficacia delle terapie non insuliniche

– Limitazioni di impiego (effetti collaterali, funzionalità d'organo, procedure diagnostiche)

– Effetto anabolico/anticatabolico dell'insulina

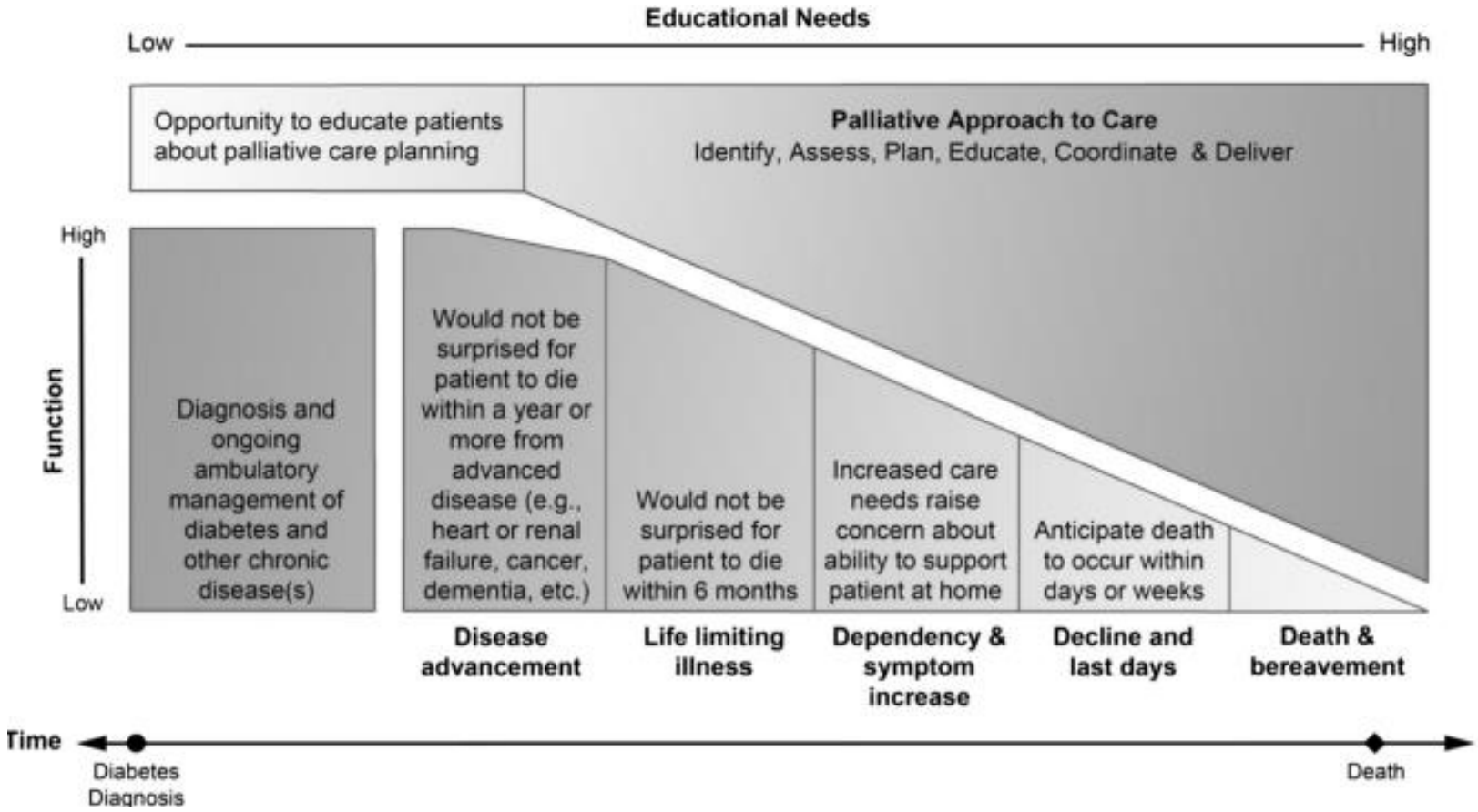
INTERAZIONI A LIVELLO DEGLI ENZIMI DEL CITOCROMO P450: SELEZIONE DI SUBSTRATI RILEVANTI PER I QUALI, QUANDO UTILIZZATI IN COMBINAZIONE CON INIBITORI O INDUTTORI DELLO STESSO ENZIMA, SI DEVE PREVEDERE UN AUMENTO DELL'EFFETTO E UN'AUMENTATA INCIDENZA DI EFFETTI INDESIDERATI O UNA RIDUZIONE O UNA PERDITA DELL'EFFETTO [14]

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	
Clozapina Imipraminea Mexiletina Naprossene Tacrina Teofillina	**FANS** Celecoxib Diclofenac Ibuprofene Naprossene Piroxicam **Antidiabetici** Glipizide Tolbutamide **Bloccanti recettori angiotensina** Irbesartan Lorsartan **Miscellanea** Ciclofosfamide Fluvastatina Fenitoina Sulfametossazolo Torasemide Warfarin	**Inibitori di pompa Protonioca** Omeprazolo Lansoprazolo **Miscellanea** Amitriptilina Clomipramina Clopidogrel* Ciclofosfamide* Diazepam Fenitoina	**Beta-bloccanti** Metoprololo Propafenone Timololo **Antidepressivi** Amitriptilina Clomipramina Desipramina Duloxetina Imipramina Paroxetina Venlafaxina **Antipsicotici** Aripiprazolo Aloperidolo Risperidone Tioridazina **Oppioidi** Codeina* Destrometorfano Tramadolo* **Miscellanea** Ondansetron Tamoxifene*	**Macrolidi** Claritromicina Eritromicina **Benzodiazepine** Alprazolam Diazepam Midazolam Triazolam **Calcioantagonisti** Amlodipina Diltiazem Felodipina Nifedipina Nisoldipina Nitrendipina Verapamil **Immunosoppressori** Ciclosporina Tacrolimus Sirolimus **Inibitori proteasi dell'HIV** Indinavir Ritonavir Saquinavir	**Statine** Atorvastatina Lovastatina Simvastatina **Anticoagulanti** Apixaban Rivaroxaban Fenprocumone **Miscellanea** Aripiprazolo Buspirone Chinidina Chinina Etinilestradiolo Imatinib Sildenafil Tamoxifene Vincristina

*Profarmaco

- La glicemia va controllata durante le terapie oncologiche, al pari della funzionalità midollare, renale ed epatica
- Un aspetto particolare del rapporto Diabete e Cancro va ricercata nelle situazioni di terminalità quando all'uso molto comune di corticosteroidi e progestinici si associano in generale condizioni di malnutrizione e di disidratazione

Gestione del DM nel fine vita



- ✓ Aumento dei fabbisogni educativi per pazienti e caregiver
- ✓ Aumento dei bisogni di supporto emozionale e di scelta
- ✓ Riduzione della medicalizzazione privilegiando in Comfort

G.M. Johnston et al. / Can J Diabetes 39 (2015) 29–35

ESMO HANDBOOK OF **CANCER TREATMENTS IN SPECIAL CLINICAL SITUATIONS**

GOOD SCIENCE
BETTER MEDICINE
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European Society for Medical Oncology

General statements regarding diabetes and cancer

- Despite higher risks of toxicities, "a priori" dose adjustments or specific anti-cancer treatment selection are not recommended on the basis of having concomitant diabetes, but close monitoring of side effects is necessary
- Diabetes mellitus (DM) increases the risk of cardiovascular events and the susceptibility to infections, both relevant for cancer patients
- Healing may be impaired in patients with DM, resulting in higher rates of postoperative complications

Practical hints in cancer patients with diabetes

- Hypertension is a common problem. Target blood pressure for patients with DM is <130/80 mmHg
- Monitor dyslipidaemia, especially in patients receiving hormonal treatments
- Chemotherapy-related neuropathy tends to appear at lower cumulative doses in patients with DM
- Risk of renal toxicity when receiving platinum-based therapies is higher for diabetic patients
- Local infections like paronychia, folliculitis or gingivitis are commonly associated with some anti-cancer agents, and these infections may be more difficult to resolve in diabetic patients, leading to systemic infections
- Use lower doses of steroids throughout the day when possible, instead of a high-dose daily bolus
- Remember to adjust anti-diabetic treatment when starting steroids. Postprandial glycaemia should be monitored in addition to fasting values

Standard italiani per la cura del diabete mellito 2018

Nell'impostazione del target glicemico e della terapia del diabete è fondamentale tenere in considerazione la condizione tumorale e la prognosi. Per il raggiungimento di appropriati livelli assistenziali è determinante la collaborazione con gli oncologi e le altre figure specialistiche coinvolte. *VI A*

La terapia insulinica è una scelta vantaggiosa per la maggior parte dei pazienti oncologici, ma non esistono evidenze conclusive per modificare a priori la scelta della terapia antidiabetica in un paziente oncologico. *VI B*

Alcune terapie antitumorali possono influenzare sfavorevolmente il compenso glicemico, quello lipidico e/o quello pressorio. La stima del rischio cardiovascolare individuale deve tenere in considerazione la situazione complessiva e l'aspettativa di vita prevista. *I B*

La presenza di diabete in un paziente oncologico non giustifica "a priori" variazioni delle terapie antitumorali o delle dosi da utilizzare. È tuttavia necessario un attento monitoraggio degli eventi avversi, in considerazione del rischio più elevato di tossicità. *IV B*

Alcune terapie antitumorali possono peggiorare la funzionalità renale o determinare neuropatia a dosi inferiori, nelle persone con diabete. È raccomandato un più stretto monitoraggio della velocità di filtrazione glomerulare e dell'albuminuria. *IV B*

Effettuare la vaccinazione influenzale annuale e quella pneumococcica indipendentemente dall'età, nei pazienti oncologici con diabete. *III B*

Conclusioni

- Diabete e Tumore possono viaggiare di pari passo dal rischio, alla diagnosi, dalle cure alla prognosi

- L'età sempre più avanzata della popolazione pone ai noi Oncologi il problema di curare sempre più pazienti diabetici così come l'avvento dei nuovi farmaci porta a tossicità sempre nuove e di difficile gestione

- Obiettivo di cura oncologica e Target glicemico in relazione alla complessità del malato ed ai suoi bisogni sono elementi che dovrebbero sempre dialogare

- La multidisciplinarietà è essenziale per la gestione dei malati oncologici con diabete per l'ottimizzazione delle cure, per l'educazione del paziente e per la prevenzione delle complicanze

grazie per l’attenzione…