Associazione Italiana
Radioterapia Oncologica
Gruppo Interregionale
Lazio/Abruzzo/Molise

Le terapie di supporto in Radioterapia:
Verso una Guida Pratica

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Tossicità nei trattamenti dell'Apparato Gastroenterico

Nausea, Vomito e Tossicità epatologica: Presidi di prevenzione e trattamento delle tossicità

Gian Carlo Mattiucci

Gemelli
Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore
ART
Advanced Radiation Therapy

Bullet points

- Radiotherapy-induced nausea and vomiting **RINV**
- Radiation-induced Liver Disease **RILD**

RINV:
Radiotherapy-induced nausea and vomiting

RINV: Under-treated

Less patients receive antiemetic prophylaxis

The risk levels depend on:

- site of radiation

do not take into account :

- radiation dose,
- fractionation
- technique
- other proposed risk factors such as field size

The only identified patient-related risk factor for RINV is:

- the previous treatment with chemotherapy

F. Roila, Annals of Oncology 2016
MASCC and ESMO Guideline

RINV:
Radiotherapy-induced nausea and vomiting

DEXAMETHASONE
(Soldesam, Decadron)

NK1 Receprtor Antagonist
(aprepitant, fosaprepitant, rolapitant)

Dopamine
Receptor Antagonist
(metoclopramide)

5-HT3 Receptor Antagonist
(ondansetron, granisetron, dolasetron)

RINV:
Radiotherapy-induced nausea and vomiting

Emetic risk levels	
HIGH (>90%)	Total body irradiation
Moderate (60-90%)	Upper abdomen, craniospinal
Low (30 - 60%)	Cranium, Head and neck, Thorax, Pelvis region
Minimal (< 30 %)	Extremities, breast

F. Roila, Annals of Oncology 2016
MASCC and ESMO Guideline

RINV:
Radiotherapy-induced nausea and vomiting

antiemetic guidelines

HIGH (>90%)	Prophylaxis with a 5-HT3-RA+DEX (II B)
Moderate (60-90%)	Prophylaxis with a 5-HT3RA +/-optional DEX (II A)
Low (30 - 60%)	Prophylaxis or rescue with 5-HT3-RA or DEX or dopamine RA (IV D))
Minimal (< 30 %)	Rescue with DEX or dopamine RA or 5-HT3-RA (IV D)

F. Roila, Annals of Oncology 2016
MASCC and ESMO Guideline

Table 5: Key recommendations of antiemetic guideline groups adapted from [1, 7].

Risk category	Dose	Schedule
	High emetic risk	
5-HT_3 receptor antagonist		5-HT_3 receptor antagonist before each fraction throughout XRT, continued for at least 24 hours after completion of XRT
Granisetron*	2 mg orally; 1 mg or 0.01 mg/kg i.v.	
Ondansetron*	8 mg orally twice daily; 8 mg or 0.15 mg/kg i.v.	
Palonosetron†	0.50 mg orally; 0.25 mg i.v.	
Dolasetron	100 mg orally only	
Tropisetron	5 mg orally or i.v.	
Corticosteroid		
Dexamethasone	4 mg orally or i.v.	During fractions 1–5
	Moderate emetic risk	
5-HT_3 receptor antagonist	Any of the above listed agents are acceptable; note preferred options†	5-HT_3 receptor antagonist before each fraction throughout XRT
Corticosteroid		
Dexamethasone	4 mg i.v. or orally	During fractions 1–5
	Low emetic risk	
5-HT_3 receptor antagonist	Any of the above listed agents are acceptable; note preferred options	5-HT_3 receptor antagonist as either rescue or prophylaxis; if rescue is used, then prophylactic therapy should be given until the end of XRT
	Minimal emetic risk	
5-HT_3 receptor antagonist	Any of the above listed agents are acceptable; note preferred options	Patients should be offered either class as rescue therapy; if rescue is used, then prophylactic therapy should be given until the end of XRT
Dopamine receptor antagonist		
Metoclopramide	20 mg orally	
Prochlorperazine	10 orally or i.v.	

*Preferred agents; †no data are currently available on the appropriate dosing frequency with palonosetron in this setting. The Update Committee suggests that dosing every second or third day may be appropriate for this agent.
5-HT_3 = 5-hydroxytryptamine-3; i.v., = intravenously; XRT = radiation therapy.

Petra Feyer, BioMed Research International 2013

RINV:
Radiotherapy-induced nausea and vomiting

Emetic risk levels

RTCT

Depends on CT scheme

F. Roila, Annals of Oncology 2016
MASCC and ESMO Guideline

CINV:
Chemotherapy-induced nausea and vomiting

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NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC <4[d] • Carmustine[d] ≤250 mg/m²	• Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[d] • Daunorubicin[d] • Dinutuximab • Doxorubicin[d] <60 mg/m² • Epirubicin[d] ≤90 mg/m² • Idarubicin	• Ifosfamide[d] <2 g/m² per dose • Interferon alfa ≥10 million IU/m² • Irinotecan[d] • Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin[d] • Temozolomide • Trabectedin[d]

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2010;19:S43-47.

Low Emetic Risk (See AE-3)

Minimal Emetic Risk (See AE-3)

Oral Chemotherapy (See AE-4)

[a]Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
[b]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[c]Continuous infusion may make an agent less emetogenic.
[d]These agents may be highly emetogenic in certain patients.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CINV:
Chemotherapy-induced nausea and vomiting

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NCCN Guidelines Version 2.2017
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
Low emetic risk (10%–30% frequency of emesis)[b]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Atezolizumab • Belinostat • Blinatumomab • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (low dose) 100–200 mg/m² • Docetaxel • Doxorubicin (liposomal)	• Eribulin • Etoposide • 5-FU • Floxuridine • Gemcitabine • Interferon alfa >5 - <10 million international units/m² • Irinotecan (liposomal) • Ixabepilone • Methotrexate >50 mg/m² - <250 mg/m² • Mitomycin • Mitoxantrone	• Necitumumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Talimogene laherparepvec • Thiotepa • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b]	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine <100 mg/m² • Daratumumab • Decitabine • Denileukin diftitox • Dexrazoxane	• Elotuzumab • Fludarabine • Interferon alpha ≤5 million IU/m² • Ipilimumab • Methotrexate ≤50 mg/m² • Nelarabine • Nivolumab • Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase	• Peginterferon • Pembrolizumab • Pertuzumab • Ramucirumab • Rituximab • Siltuximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2010;19:S43-47.

High Emetic Risk (See AE-2)
Moderate Emetic Risk (See AE-2)
Oral Chemotherapy (See AE-4)

[a]Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
[b]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CINV:
Chemotherapy-induced nausea and vomiting

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NCCN Guidelines Version 2.2017
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF ORAL ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
Moderate to high emetic risk[b] (≥30% frequency of emesis)	• Altretamine • Busulfan (≥4 mg/d) • Ceritinib • Crizotinib • Cyclophosphamide (≥100 mg/m²/d)	• Estramustine • Etoposide • Lenvatinib • Lomustine (single day) • Mitotane	• Olaparib • Panobinostat • Procarbazine • Rucaparib • Temozolomide (>75 mg/m²/d) • Trifluridine/tipiracil
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Afatinib • Alectinib • Axitinib • Bexarotene • Bosutinib • Busulfan (<4 mg/d) • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide (<100 mg/m²/d) • Dasatinib • Dabrafenib • Erlotinib • Everolimus • Fludarabine	• Gefitinib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib • Ixazomib • Lapatinib • Lenalidomide • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Osimertinib • Palbociclib • Pazopanib • Pomalidomide • Ponatinib	• Regorafenib • Ruxolitinib • Sonidegib • Sorafenib • Sunitinib • Temozolomide (≤75 mg/m²/d)[e] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2010;19:S43-47.

High Emetic Risk (See AE-2)
Moderate Emetic Risk (See AE-2)
Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)

[a]Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
[b]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[e]Temozolomide ≤75 mg/m²/d should be considered moderately emetogenic with concurrent radiotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CINV:
Chemotherapy-induced nausea and vomiting

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select option A, B, C, D, E, F (order does not imply preference) All are category 1, start before chemotherapy:[h]	**DAYS 2, 3, 4:**
A: • Aprepitant 125 mg PO once • 5-HT3 RA (choose one): ▸ Palonosetron 0.25 mg IV once ▸ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ▸ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ▸ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	A:[v] • Aprepitant 80 mg PO daily on days 2, 3 • Dexamethasone 8 mg[l,m] PO/IV daily on days 2, 3, 4
B: • Fosaprepitant 150 mg IV once • 5-HT3 RA (choose one): ▸ Palonosetron 0.25 mg IV once ▸ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ▸ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ▸ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	B:[v] • Dexamethasone 8 mg[l,m] PO/IV daily on day 2, then dexamethasone 8 mg[l,m] PO/IV twice daily on days 3, 4
C: • Rolapitant 180 mg PO once[n,o] • 5-HT3 RA (choose one): ▸ Palonosetron 0.25 mg IV once ▸ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ▸ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ▸ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	C:[v] • Dexamethasone 8 mg[l,m] PO/IV twice daily on days 2, 3, 4
D: • Netupitant 300 mg/palonosetron 0.5 mg PO once[p,q] • Dexamethasone 12 mg PO/IV once[l,m]	D: • Dexamethasone 8 mg[l,m] PO daily on days 2, 3, 4
E: • Olanzapine 10 mg PO once[r,s] • Palonosetron 0.25 mg IV once • Dexamethasone 20 mg IV once[m]	E: • Olanzapine 10 mg PO daily on days 2, 3, 4[s]
F: • Aprepitant 125 mg PO once or fosaprepitant 150 mg IV once[t,u] • 5-HT3 RA (choose one): ▸ Palonosetron 0.25 mg IV once ▸ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ▸ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ▸ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m] • Olanzapine 10 mg PO once[s]	F:[v] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant on day 1) • Dexamethasone 8 mg[l,m] PO/IV daily on days 2, 3, 4 • Olanzapine 10 mg PO daily on days 2, 3, 4[s]

See Breakthrough Treatment (AE-10)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See Footnotes (AE-7)

RILD:
Radiation-induced liver disease

Therapy

- **No therapy has been shown to prevent or to modify the natural course of the disease**

Prophilaxis = Respect Constraints

RILD:
Radiation-induced liver disease

Constraints – Whole liver irradiation

Ingold JA, et al. 1965:
Ascites and hepatomegaly in 1 of 8 patients who received 30–35 Gy over 3–4 weeks versus 12 of 27 patients who received >35 Gy

Emami B, *et al.* 1991:
The whole liver tolerance dose expected to yield a 5% risk of liver failure 5 years after treatment (TD 5/5) for whole liver radiation was estimated to be 30 Gy in 2 Gy fractions

Russell AH, et al. 1993:
0/122 patients who received 27–30 Gy in twice daily 1.5 Gy fractions of whole liver RT experienced severe RILD,
5/51 who received 33 Gy in 1.5 Gy fractions developed RILD

Chandan Guha, Semin Radiat Oncol. 2011

RILD:
Radiation-induced liver disease

Constraints – Partial liver irradiation

mean liver dose was <31 Gy (EQD2): No RILD

numerous reports demonstrating a higher risk of toxicity among patients with worse baseline liver dysfunction.

Liang SX, Int J Radiat Oncol Biol Phys. 2006
Xu ZY, Int J Radiat Oncol Biol Phys. 2006
Liang SX, Cancer 2005
Hata M, Strahlenther Onkol. 2006

RILD:
Radiation-induced liver disease

Therapy

- **No therapy has been shown to prevent or to modify the natural course of the disease**
- **Treatment is mainly directed at control of symptoms (diuretics for fluid retention, paracentesis for ascites, correction of coagulopathy, and steroids to reduce hepatic congestion)**
- **Glutathione plays a protective role in preventing SOS caused by irradiation and chemotherapeutic agents**

Chandan Guha, Semin Radiat Oncol. 2011

RILD:
Radiation-induced liver disease

Strategies to prevent or minimize radiation-induced hepatotoxicity

Various strategies are being investigated to inhibit stellate cell activation and reverse fibrosis in RILD:

- **Anti-TGF-β therapy** with monoclonal antibodies against TGF-β and several small molecular agents that inhibit the kinase activity of TGF-β receptors are being investigated to reverse chronic liver fibrosi.
(TGF-β showed a radiation dose dependent increase, and suppression of TGF-β was reported to reduce hepatic fibrosis in the irradiated livers of experimental animals. Thus, anti-TGF-βtherapy is a therapeutic strategy against RILD development).

- **Defibrotide** is a complex mixture of single-stranded polydeoxyribonucleotides that is approved in the United States for treating hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT (hematopoietic stem cell transplantation)

Chandan Guha , Semin Radiat Oncol. 2011 October
Paul G. Richardson, Biol Blood Marrow Transplant 2017

RILD:
Radiation-induced liver disease

Strategies to prevent or minimize radiation-induced hepatotoxicity

- **Stem cell-based therapy**:
  - ameliorate the unintended side effects in normal tissues exposed to radiation by promoting the regeneration of irradiated normal tissues

- The **infusion of mesenchymal stem cell** (MSC) / MSC-derived bioactive components
  - prevent radiation-induced liver injury by inhibiting both apoptosis and inflammation in experimental animals.

Chandan Guha, Semin Radiat Oncol. 2011

RILD:
Radiation-induced liver disease

Summary

- Mean radiation dose of 30 Gy is considered as safe but radiation tolerance of liver decreases in the presence of deranged liver functions.
- Newer techniques of radiation have reduced the incidence of RILD,
- Prevention is the key as there are no specific treatment guidelines. Attempt should be made to keep the mean dose below tolerance level.
- Indicator of liver function status like Child-Pugh score is an important parameter to predict the toxicity.

- Role of radio-protectors is doubtful.
- More extensive research is required to structure guidelines for prevention and management.