Regimen Monograph

A - Regimen Name

CAPEGEMC Regimen

Gemcitabine-Capecitabine

Disease Site Gastrointestinal
Pancreas

Intent Adjuvant

Regimen Category **Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Supplementary Public Funding **capecitabine**
ODB - General Benefit (capecitabine)

back to top

B - Drug Regimen

gemcitabine	1000 mg /m²	IV	Days 1, 8 and 15
capecitabine	830 mg /m²	PO	BID days 1 to 21

(*Total daily dose 1660 mg/m2/day; Outpatient prescription in 150mg and 500mg tablets)

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low
No routine prophylaxis for capecitabine

Other Supportive Care:

- Topical emollients (e.g. hand creams, udder balm) therapy may ameliorate the manifestations of hand-foot syndrome related to capecitabine.
- Supportive care should be provided, including loperamide for diarrhea.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

The following capecitabine dose banding was used in the ESPAC-4 trial:

BSA (m^2)	Total daily dose (mg)	Number of tablets Administered in the AM		Number of tablets administered in the PM	
		150mg	500mg	150mg	500mg
<1.60	2500	0	2	0	3
1.60-1.80	2800	1	2	1	3
>1.80	3300	1	3	1	3

Dosage with toxicity

Hematologic toxicity:

Doses of capecitabine generally do not require modifying for hematologic toxicity.

Dose of Gemcitabine on Day 1, 8 or 15:

Absolute neutrophil count ($x10^9$/L)		Platelet Count (x 10^9/L)	Gemcitabine Dose
>1.0	and/or	>100	100% of full dose
0.5 - 1.0	and/or	50 - 100	75 % of full dose
< 0.5	and/or	<50	Hold for 1 week

Clinical Scenario	Gemcitabine dose for next treatment	Capecitabine dose for next treatment
Dose reduction for 1 week	Dose according to neutrophil and/or platelet count on that day	Continue 100%
Dose reduction for 2 consecutive weeks	75% of full dose with no re-escalation	Continue 100%
Initial dose omission for 1 week	75% of full dose with no re-escalation	Continue 100%
Recurrent dose omission or delay ≥ 2 weeks	75% of full dose with no re-escalation	75% of full dose with no re-escalation

Non-hematologic toxicity:

Doses of gemcitabine generally do not require modification for non-hematologic toxicity. Gemcitabine should be discontinued if pneumonitis, Hemolytic Uremic Syndrome (HUS), Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), capillary Leak Syndrome (CLS) or PRES occur.

Capecitabine:

Toxicity†	**Action During a Course of Therapy**	**Dose Adjustment for Next Cycle (% of starting dose)**
Grade 1	Supportive measures; Maintain dose level	Maintain dose level
Grade 2 1st appearance 2nd appearance 3rd appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue	 100% 75% --
Grade 3 1st appearance 2nd appearance 3rd appearance OR any evidence of Stevens-Johnson syndrome or Toxic Epidermal Necrolysis	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 75% 50% --
Grade 4	Discontinue permanently	Discontinue

†Dose adjustment mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening. Doses should not be re-escalated if reduced for toxicity.

Hepatic Impairment

Bilirubin		AST/ALT	Capecitabine (% previous dose - suggested)	Gemcitabine (% previous dose – suggested)
< 1.5 x ULN	and/ or	<3 x ULN	100%	100%
1.5 - 3 x ULN		3-5 x ULN	Consider ↓ to 75%	Consider ↓ to 75%
> 3 x ULN		> 5 x ULN	Discontinue	Discontinue

Renal Impairment

Creatinine clearance (mL/min)	Gemcitabine (% previous dose)	Capecitabine (% previous dose)
51-80	100%	100%
30-50	100%	75%
<30	Consider discontinuing or ↓ dose	Discontinue

Dosage in the elderly:

Capecitabine: No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed as described above. Older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination.

Gemcitabine: Clearance is lower in the elderly but no dose adjustment necessary.

Dosage based on gender:

Gemcitabine clearance is lower in women but no dose adjustment necessary.

Children:

Safety and effectiveness in children have not been established.

back to top

F - Adverse Effects

Refer to capecitabine, gemcitabine drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• ↑ LFTs (may be severe) • Nausea, vomiting • Hand-foot syndrome	• Diarrhea (may be severe) • Fatigue • Flu-like symptoms • Proteinuria • Myelosuppression ± infection, bleeding (may be severe) • Rash (may be severe)	• Mucositis • Edema • Musculoskeletal pain • Alopecia • Abdominal pain	• Pneumonitis/ARDS • Hemolytic-uremic syndrome • Arrhythmia • Cardiotoxicity • Venous/arterial thromboembolism • Capillary leak syndrome • Hypersensitivity • Vasculitis • GI obstruction, perforation • Eye disorders, including keratitis • PRES

back to top

G - Interactions

Refer to capecitabine, gemcitabine drug monograph(s) for additional details

- Capecitabine is converted to active 5-FU by the enzyme DPD. The drug likely inhibits CYP2C9, resulting in possible drug interactions with CYP2C9 substrates.
- Avoid concomitant phenytoin if possible; monitor levels of phenytoin closely if cannot discontinue.
- Caution with warfarin and monitor PT and INR closely (↑ warfarin exposure).
- Avoid concomitant sorivudine and wait 4 weeks after starting before initiating capecitabine treatment (potentially fatal increase in capecitabine toxicity).

back to top

H - Drug Administration and Special Precautions

Refer to capecitabine, gemcitabine drug monograph(s) for additional details

Administration

Capecitabine:

- Oral self-administration; drug available by outpatient prescription.
- Clinical studies performed with capecitabine administered 30 minutes after food. Administering capecitabine on an empty stomach may result in slightly higher exposure and thus toxicity.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package

Gemcitabine:

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Infuse over 30 minutes through free-flowing IV. Infusion time beyond 60 minutes has been shown to increase toxicity.

Contraindications:

- Patients who have a known hypersensitivity to gemcitabine, capecitabine, their excipients, or 5-fluorouracil
- Patients with severe renal impairment (CrCl <30 mL/min)

- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction
- Capecitabine contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.

Other Warnings/Precautions:

- Patients with compromised bone marrow
- Avoid using as a prolonged gemcitabine infusion (more than 60 minutes) or more frequently than weekly since this can increase toxicity
- Patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis
- Patients receiving concurrent radiation while receiving full dose gemcitabine should be closely monitored for reactions. Potentially life-threatening esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy have been observed.
- Patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents
- Patients with a history of cardiovascular disease
- Patients taking anticoagulants such as warfarin (see Drug Interactions section)
- Patients with partial DPD deficiency - use capecitabine with extreme caution. Refer to the DPD Deficiency Guidance for Clinicians for more information.

Pregnancy and Lactation:

- Capecitabine and gemcitabine are not recommended for use in pregnancy. If there is ANY chance of pregnancy, adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Breastfeeding is not recommended.
- Fertility effects are probable for both males and females

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and at each visit
- Clinical assessment of flu-like symptoms, GI effects, CNS effects, lethargy, dyspnea, rash, diarrhea, dehydration, infection, stomatitis, rash or hand-foot syndrome, cardiac, hepatic and neurotoxicity; At each visit
- INR and/or PT; Baseline and regular if on anticoagulants
- Liver function tests; Baseline and regular
- Renal function tests; Baseline and regular

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Urinalysis; Baseline and regular

back to top

J - Administrative Information

Outpatient prescription for home administration (capecitabine)

Approximate Patient Visit	0.75 hour
Pharmacy Workload (average time per visit)	22.85 minutes
Nursing Workload (average time per visit)	36.667 minutes

back to top

K - References

Capecitabine and gemcitabine drug monographs, Cancer Care Ontario.

Neoptolemos JP et al. ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP)

versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma. J Clin Oncol 34, 2016 (suppl; abstr LBA4006)

PEBC Advice Documents or Guidelines

- Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top