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Conference Review

Gastrointestinal malignancies: eGurukul drug capsules

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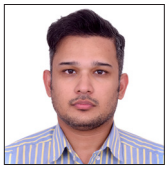

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The Gurukul series is a resident-led academic initiative designed to bridge the gap between textbook oncology and the nuanced realities of clinical chemotherapy practice. Anchored in peer-to-peer learning and supported by expert national faculty, the series delivers high-yield discussions emphasizing decision-making, drug toxicities, sequencing strategies, and context-driven modifications in therapy. Each session is tailored to integrate the multifaceted and common challenges faced during routine oncology rounds so that young oncologists are both exam and practice-ready. The following proceedings aim to serve as practical guidance for residents attempting to acclimatize themselves to the nuances of systemic cancer therapy by documenting key takeaways from the sessions.

The core pharmacotherapeutic landscape of gastrointestinal (GI) malignancies encompasses fluoropyrimidines, platinum agents, topoisomerase inhibitors, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, anti-angiogenic agents, and oral multikinase inhibitors. Oxaliplatin-based combinations such as FOLFOX and CAPEOX remain integral to managing stage III colorectal cancer, with evidence from the MOSAIC trial showing a 6% absolute improvement in five year disease free survival (DFS) when added to 5-fluorouracil (5-FU) and leucovorin. The drug's hallmark toxicity is peripheral neuropathy – acute cold-induced paresthesia due to sodium channel dysfunction and chronic cumulative neuropathy linked to dorsal root ganglion injury. The acute laryngeal dysesthesia is a unique side effect of Oxaliplatin characterized by transient throat tightness, dysphagia or dyspnea triggered by cold exposure and observed within hours to three days of therapy. Although it occurs in just ~2% of patients, it can be alarming to them. It is self-limiting and managed with reassurance, slow infusion and avoidance of cold liquids. Paresthesias are cumulative, dose-related, and reversible with recovery beginning at 13 weeks of last therapy. Neuropathy interfering with function becomes apparent only after four months of therapy and doses above 800 mg/m^2 are associated with irreversible symptoms. Strategies such as "stop-and-go" (e.g., OPTIMOX regimen) help preserve efficacy while reducing chronic toxicity risk. Oxaliplatin should be avoided in patients with creatinine clearance (CrCl) <30 mL/min and used cautiously in CrCl 30–50 mL/min. Notably, Oxaliplatin must be diluted in 5% dextrose to avoid its degradation.

Irinotecan, a prodrug activated to SN-38, a potent topoisomerase I inhibitor, is central to regimens such as FOLFIRI and FOLFOXIRI. The CALGB 80405 trial validated irinotecan-based regimens in metastatic colorectal cancer (mCRC) with a median overall survival (OS) of 29 months when combined with bevacizumab or cetuximab. Irinotecan-induced diarrhea remains a significant dose-limiting toxicity and must be rigorously stratified by timing and mechanism. Early-

onset diarrhea, occurring within 24 h, is due to cholinergic overstimulation. The standard intervention is atropine 0.25–1 mg subcutaneously, administered either prophylactically or at first symptom onset. Late-onset diarrhea, typically beginning after 24 h and often peaking around day 5–7, results from mucosal epithelial injury mediated by the active metabolite SN-38. It is managed with high-dose loperamide: An initial dose of 4 mg, followed by 2 mg every 2 h, continuing until 12 h after the last unformed stool, with a maximum of 16 mg/day in standard use but up to 24 mg/day under oncology-directed protocols. Persistent Grade ≥2 diarrhea despite 24 h of loperamide mandates escalation to octreotide 100–150 mcg subcutaneously 3 times daily. Genetic polymorphisms, especially UGT1A1*28, impair SN-38 glucuronidation and predispose to neutropenia and diarrhea – genotyping is advised in high-risk populations. Dose adjustment is mandatory in hepatic dysfunction or bilirubin elevation.

Fluoropyrimidines, including intravenous 5-FU and oral capecitabine, inhibit thymidylate synthase, thereby impairing deoxyribonucleic acid (DNA) synthesis. Infusional 5-FU leads to mucositis, diarrhea, and hand-foot syndrome (HFS), whereas bolus 5-FU causes more pronounced myelosuppression. The pre-treatment cardiac assessment is required in all patients planned for fluoropyrimidines especially the ones with a history of CAD, arrhythmia, or previous chest radiation. Cardiotoxicity incidence is ~4%, with presentations ranging from silent electrocardiogram changes to ST-elevation myocardial infarction. Prophylaxis with diltiazem 60 mg thrice daily or isosorbide mononitrate 30–60 mg daily is recommended in high-risk individuals. If cardiotoxicity is suspected, immediate discontinuation of 5-FU and cardiology referral is warranted. Re-challenge is controversial and should only be done under telemetry in a monitored setting.

The X-ACT trial confirmed that capecitabine is non-inferior to 5-FU in the adjuvant setting, with improved tolerability. Importantly, capecitabine interacts with CYP2C9 substrates like warfarin, increasing bleeding risk. Capecitabine can cause HFS or palmar-plantar erythrodysesthesia refers to a condition where the palms of the hands and soles of the feet become dry, furrowed, red, numb, and tingling, with or without associated swelling. The patients should be advised to apply lanolin/urea/diclofenac-containing creams liberally and frequently to palms and soles. Capecitabine requires renal dose modification:

- CrCl 30–50 mL/min: Reduce dose to 75%
- CrCl <30 mL/min: Contraindicated
- Dose rounding must be precise due to narrow toxicity margins, especially in elderly or frail patients.

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency significantly increases toxicity risk and mandates pretreatment testing in select populations. Both 5-FU and capecitabine are associated with cardiotoxicity, including vasospasm, arrhythmias, and myocardial infarction – often independent of pre-existing cardiac disease. Trifluridine (a nucleoside metabolic inhibitor) + Tipiracil (a thymidine phosphorylase inhibitor) once inside the cell, Trifluridine is phosphorylated by thymidine kinase and incorporated into DNA → interfering with DNA synthesis and preventing cell proliferation. Tipiracil enhances the oral availability of trifluridine by inhibiting its rapid degradation and subsequent first-pass metabolism by thymidine phosphorylase. Although trifluridine is a fluoropyrimidine, it is metabolized by thymidine phosphorylase rather than DPD and as a result, its dosing is not affected by DPD deficiency.

In general, chemotherapy is held or reduced for toxicities as per institutional CTCAE thresholds:

- Absolute neutrophil count (ANC) <1500/μL or platelet <100,000/μL: Hold cycle
- Re-initiate once counts recover; for repeated cytopenias, reduce chemotherapy dose by 25%
- Grade 3 diarrhea or mucositis: Hold until recovery to ≤ Grade 1, then resume at 75% dose

Anti-EGFR monoclonal antibodies – cetuximab (chimeric immunoglobulin G [IgG]1) and panitumumab (fully human IgG2) – are effective only in RAS wild-type mCRC. Cetuximab induces ADCC and is more immunogenic, requiring premedication. Both agents are associated with high rates of dermatologic toxicity, particularly acneiform rash and paronychia. The presence of rash often correlates with a better response. Electrolyte derangements, notably hypomagnesemia and hypokalemia, necessitate regular monitoring. Infusion-related anaphylaxis (particularly with cetuximab) is geographically linked to preformed anti-galactose-α-1,3-galactose immunoglobulin E (IgE) antibodies and mandates first-dose vigilance. Anti-EGFR agents such as cetuximab require pre-medication with chlorpheniramine 10 mg IV, diphenhydramine 50 mg IV, and corticosteroids if prior reactions occur. Infusion reactions may occur in up to 20% of first doses, particularly in regions with high prevalence of anti–alpha-gal IgE (e.g., Southern US, India). EGFR inhibitor-induced dermatologic toxicity, particularly the characteristic acneiform papulopustular rash (typically appearing within 7–10 days), is both a predictive biomarker and a management challenge. Prophylactic measures include:

- Oral doxycycline 100 mg twice daily or minocycline 100 mg once daily
- Topical hydrocortisone 1% or clindamycin 1% gel once or twice daily
- Alcohol-free emollients applied twice daily
- A broad-spectrum sunscreen with SPF ≥30.

The rash typically peaks by week 4, and severity is graded as per CTCAE v5.0:

- Grade 1: <10% body surface area (BSA), no impact on activities of daily living (ADL)
- Grade 2: 10–30% BSA, some interference
- Grade 3: >30% BSA, limiting self-care.

Grade ≥2 requires continuation with supportive care, but Grade 3 rash may necessitate dose delay, reduction, or temporary discontinuation.

The multikinase inhibitor regorafenib acts on VEGFR, PDGFR, RAF, and FGFR pathways and is approved for refractory mCRC. Hand foot skin reaction, diarrhea, hypertension, and hepatotoxicity are predominant adverse effects. Weekly dose escalation (starting from 80 mg) improves tolerability. Regorafenib is metabolized through CYP3A4, and its co-administration with inducers (rifampin) or inhibitors (azoles) alters drug exposure, necessitating dose adjustment. Similarly, TAS-102, a fixed combination of trifluridine and tipiracil, offers OS benefit in third-line mCRC (RECOURSE trial: 7.1 vs. 5.3 months). Unlike 5-FU, its efficacy is not influenced by DPD status, offering a therapeutic advantage in DPD-deficient patients. Hematologic toxicities, particularly neutropenia, require close monitoring and may necessitate G-CSF support.

Ramucirumab, an anti-VEGFR2 monoclonal antibody, has shown benefit in advanced gastric and gastroesophageal junction cancers, particularly when combined with paclitaxel. It carries risks of hypertension, proteinuria, arterial thromboembolism, and GI perforation. H1 antagonists and corticosteroid premedication manage infusion reactions. Renal and bleeding complications require prompt discontinuation in high-grade events.

Residents must memorize numeric cutoffs, toxicity grading schemes, and stepwise rescue strategies. For trainees, these principles form the bedrock of clinical readiness in modern-day GI oncology.

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