PROGNOSTIC FACTORS FOR ADVERSE EVENTS

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TRIAL SUMMARY: Predicting toxicities

Watanabe A, Yang C, Cheung WY Baseline characteristics as predictors of adjuvant chemotherapy (AC) toxicities in stage III colorectal cancer (CRC) patients. Canadian Association of Medical Oncology, Abstract 21, April 27, 2017, Toronto

For patients on chemotherapy, toxicities can lead to declining health status and poor adherence. This study examines associations between baseline characteristics and toxicity in 371 patients with colorectal cancer (CRC) treated with adjuvant monotherapy (capecitabine) or combination therapy (FOLFOX or CAPOX) within 12 weeks of curative resection. Median age was 65 years, 52% were men, 14% were Eastern Cooperative Oncology Group (ECOG) status ≥2, 41% received monotherapy, and 59% received combination therapy.

Results: For monotherapy, univariate analyses found that age, sex, ECOG status and pretreatment anemia were associated with hematologic toxicities, and tumour location was associated with gastrointestinal (GI) toxicities ($p<0.05$). On multivariate analyses, hematological toxicities were predicted by age ≥70 (OR=3.30, 95% CI: 1.17, 9.37; p=0.025) and pre-treatment anemia (OR=23.18, 95% CI: 6.36, 84.48; p= 0.000), while GI toxicities were less likely to occur with a tumour site at or after the splenic flexure (OR=0.38, 95% CI: 0.15, 0.99, p=0.047). For combination therapy, sex and pretreatment anemia were associated in univariate analyses with hematologic toxicities, while cardiac and/or respiratory comorbidities were associated with neuropathy ($p< 0.05$). In multivariate analyses, only female sex was predictive of hematologic toxicities (OR=5.13, 95% CI: 2.08, 12.68, p=0.000) and neuropathy was less likely to develop in patients with cardiac and/or respiratory comorbidities (OR=0.23, 95% CI: 0.07, 0.81, p=0.023). The authors consider that these associations should be discussed with patients when contemplating AC.

IN BRIEF

Already known
- Chemotherapy toxicities contribute to declining health and poor adherence.

What this study showed.
- Certain baseline characteristics are associated with increased risk for particular toxicities.

Next steps
- Consider particular associations when discussing adjuvant chemotherapy with patients.

TRIAL SUMMARY: Acute cognitive impairment

Khan OF, Cusano E, Raissouni S, et al. Immediate-term chemotherapy-related cognitive impairment (CRCI) following administration of intravenous (IV) chemotherapy. Canadian Association of Medical Oncology, Abstract 23, April 27, 2017, Toronto

This study assessed the acute impact of chemotherapy on cognition in 144 patients receiving first-line IV chemotherapy for any stage breast (n=74) or colorectal (n=70) cancer. Median age was 55.5 years. Patients with brain metastases, neurologic disorders or allergic reactions to chemotherapy were excluded. Patient symptoms, peripheral neuropathy and Stanford Sleepiness Scale were assessed. A 5-minute psychomotor vigilance task (PVT) and trail-making test B (TMT) were completed on a tablet computer prechemotherapy and immediately postchemotherapy. Paired Wilcoxon Rank Sum tests were used to assess change in median PVT reaction time, TMT completion time, TMT errors and PVT lapses. A >20 ms increase in median PVT reaction times was considered clinically relevant.

IN BRIEF

Already known
- Cumulative chemotherapy can lead to cognitive impairment in some patients.

What this study showed
- Psychomotor vigilance task (PVT) reaction time was slowed significantly in 41% of patients immediately following chemotherapy administration.
- This effect appeared independent of age or self-reported symptoms.

Next steps
- Further studies should assess the functional impact of immediate-term chemotherapy-related cognitive impairment.

Results: Median PVT reaction time slowed by an average of 12.4 ms (p=0.01) post chemotherapy, while in 59 patients (40.9%), median PVT times slowed by over 20 ms. TMT completion post chemotherapy was faster by an average of 6.1 seconds (p<0.001). No differences were seen in TMT errors (p=0.417) or PVT lapses (p=0.845). Change in median PVT reaction time was not associated with age, gender, number of prior chemotherapy cycles, use of paclitaxel (which contains alcohol), peripheral neuropathy, or self-reported anxiety, fatigue or depression. Findings indicate that median PVT reaction time slowed significantly immediately after chemotherapy compared to a pre-chemotherapy baseline, and impairment correlating to alcohol consumption was seen in 41% of patients.

TRIAL SUMMARY: Ipilimumab and diarrhea/colitis

Iafolla MAJ, Pond GR, McWhirter E. Retrospective analysis of ipilimumab-induced diarrhea and/or colitis: a single-centre review. Canadian Association of Medical Oncology, Abstract 42, April 27, 2017, Toronto

Ipilimumab is an effective medication in advanced melanoma but can cause severe diarrhea and colitis. This retrospective study, using the Ontario Patient Information System, included all melanoma patients (n=71) at the Juravinski Cancer Centre (JCC) who were treated with ipilimumab 3 mg/kg IV every 3 weeks between September 2012 and June 2016. Authors identified the rate of ipilimumab-induced diarrhea/colitis, factors associated with its development, and interventions used to treat it, and looked at overall survival (OS) and progression-free survival (PFS). Descriptive statistics summarized characteristics and outcomes. Kaplan-Meier methods were used to estimate time to event outcomes. Cox regression evaluated whether markers were prognostic for time to diarrhea/colitis diagnosis.

Results: Of the 71 patients treated with ipilimumab, 22 (31%) developed diarrhea/colitis. Eleven patients required prednisone 1–2 mg/kg and 2 patients required anti-tumour necrosis factor TNF treatment to treat their diarrhea/colitis; 1 patient required colectomy due to perforation. Ipilimumab was discontinued due to diarrhea/colitis in 10 patients.

Median OS and PFS in the cohort were 340 days (95% CI: 205, 519) and 110 days (95% CI: 91,138), respectively. Univariate analysis showed that only inadequate hematologic function at the time of first ipilimumab application was prognostic of diarrhea/colitis (HR=6.42, 95% CI: 1.44, 28.62; p=0.015).

IN BRIEF

Already known
- Ipilimumab is effective in melanoma, but can cause diarrhea and colitis.

What this study showed
- Real-world experience with ipilimumab in one centre showed rates of diarrhea/colitis similar to those seen in clinical trials, but a greater proportion of severe effects.

Next steps
- Undertake further studies to identify risk factors for the development of this immune-related adverse event.

TRIAL SUMMARY: Cardiotoxicity with trastuzumab

Tyagi NK, Arora R, Partridge ACR, et al. Rates of trastuzumab-associated cardiotoxicity in HER2-positive breast cancer patients at a tertiary cancer centre. Canadian Association of Medical Oncology, Abstract 56, April 27, 2017, Toronto

Human epidermal growth factor receptor 2 (HER2) is overexpressed in 15% to 25% of breast cancers and is associated with decreased rates of survival. Trastuzumab is a humanized monoclonal antibody that binds against HER2 and improves both disease-free survival (DFS) and overall survival (OS) in the adjuvant setting. In clinical trials, between 1% and 16% of patients treated with trastuzumab experience reversible cardiotoxicity, which can lead to early treatment discontinuation. To see whether these rates are representative of clinical practice, this study identifies the rates of trastuzumab-associated cardiotoxicity and early discontinuation of trastuzumab due to cardiotoxicity at the Juravinski Cancer Centre (JCC), in Hamilton, Ontario, between 2006 and 2013. Patient charts were reviewed for relevant clinical-pathologic variables, cardiac risk factors, cardiotoxicity events/types, and number of trastuzumab cycles completed. Cardiotoxicity was defined as decreased left ventricular ejection fraction (DLVEF) of ≥15%, DLVEF of >10% to under 50%, or a cardiac event that required delay or discontinuation of trastuzumab.

Results: Of 353 identified patients, 170 (48.2%) had at least one known risk factor for cardiac disease. Cardiotoxicity

TABLE 1: Results

Events	n (%)
Completed one year adjuvant trastuzumab	232 (65.7%)
Cardiotoxicity (CT)	110 (31.2%)
Patients suffering CT who were referred to a cardiologist	22 (20.0%)
DLVEF ≥15% or >10% to under 50%	90 (25.5%)
DLVEF ≥15%	71 (20.1%)
Delay in treatment due cardiotoxicity	62 (17.6%)
Discontinued early due to cardiotoxicity	52 (14.7%)

DLVEF: decreased left ventricular ejection fraction.

was seen in 110 (31.2%) patients, and trastuzumab had to be delayed or discontinued in 17.6% and 14.7%, respectively, of patients who experienced cardiotoxicity (see **Table 1**). Rates of cardiotoxicity were found to be higher at JCC than in clinical trials, which is not unexpected, as patients with known cardiac risk factors and history of cardiac disease were excluded from most clinical trials of trastuzumab. The authors highlight the need for strategies to optimize cardiac risk factors and manage cardiotoxicity.

COMMENTARY: Adverse events are a common occurrence during treatment for malignant disease. Patients with cancer are a heterogeneous group, and it is important to identify individuals who may be particularly susceptible to treatment-related toxicity. Four abstracts presented at the Canadian Association of Medical Oncology (CAMO) annual meeting highlighted this issue and aimed to identify at risk patients.

Watanabe et al examined the association between baseline characteristics and toxicity in 371 patients with colorectal cancer treated with adjuvant therapy.[1] The authors found that age >70, pretreatment anemia and sex were predictive of hematologic toxicity in multivariable analyses. Gastrointestinal toxicities were associated with tumour location, while preexisting cardiac or respiratory comorbidities were associated with neuropathy.

Khan et al assessed the acute impact of chemotherapy on cognition in 144 patients receiving first-line chemotherapy for any stage of breast or colorectal cancer.[2] While they did note a significant decrease in the 5-minute psychomotor vigilance task after chemotherapy, this change was not associated with age, gender, number of chemotherapy cycles, presence of neuropathy, fatigue or depression.

Iafolla et al performed a retrospective analysis on the rate of ipilimumab-induced diarrhea or colitis in 71 patients with advanced melanoma.[3] In univariate analyses, inadequate hematologic function at the time of first ipilimumab treatment was associated with an increased risk of colitis, whereas no association was found with age, gender, renal function, lymphocyte concentration or lactate dehydrogenase levels.

Arora et al sought to examine the rate of cardiotoxicity associated with the use of adjuvant trastuzumab in 352 patients with HER-2 positive breast cancer.[4] They found that preexisting diabetes and past use of angiotensin-converting enzyme (ACE) inhibitors was associated with increased risk of cardiotoxicity. Factors such age, previous cardiac event, hypertension, hyperlipidemia and chemotherapy regimen were not associated with cardiotoxicity.

These abstracts highlight key factors that may predispose patients to adverse effects with the use of certain cytotoxic chemotherapies or targeted agents. Many of the analyses were exploratory in nature and did not detect any significant factors. Historically, performance status has been used to identify patients at risk for adverse events related to chemotherapy.[5] However, its use has limitations, given that the performance status assessment is subjective and can vary between clinicians.[5] These 4 abstracts, along with several examples in the literature, have shown that age, tumour, treatment type, various laboratory measurements and geriatric assessment variables are potential predictors for chemotherapy-related toxicity in certain contexts.[6] These findings may help identify at-risk populations, though additional studies are needed to further delineate optimal predictive models.

IN BRIEF

Already known

- Trastuzumab improves disease-free survival (DFS) and overall survival (OS) in the adjuvant setting in patients with HER2+ breast cancer.
- Clinical trials of trastuzumab report rates of cardiotoxicity ranging from 1% to 16%.

What this study showed

- In the real-world setting, where cardiovascular (CV) risk factors are common, the rate of trastuzumab-induced cardiotoxicity reached 31.2% — significantly higher than those seen in clinical trials, where patients with CV risk factors are excluded.

Next steps

- Undertake trials examining the feasibility of maintaining trastuzumab therapy in the setting of mildly decreased left ventricular ejection fraction (DLVEF).
- Develop strategies to optimize cardiac risk factors in patients before initiating trastuzumab.

References:

1. Watanabe A, Yang C, Cheung WY Baseline characteristics as predictors of adjuvant chemotherapy (AC) toxicities in stage III colorectal cancer (CRC) patients. Canadian Association of Medical Oncology, Abstract 21, April 27, 2017, Toronto.
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3. Iafolla MAJ, Pond GR, McWhirter E. Retrospective analysis of ipilimumab-induced diarrhea and/or colitis: a single centre review. Canadian Association of Medical Oncology, Abstract 42, April 27, 2017, Toronto.
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