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ASCO Gastrointestinal Cancers Symposium: Perspectives on Older Adults with Gastrointestinal Malignancies

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Introduction

The 2019 American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Cancers Symposium was held January 17–19 in San Francisco, California, with an attendance of ~3500 specialists. Over 700 abstracts were presented on the spectrum of GI cancers, with this year's overarching theme on "Multidisciplinary treatment, personalized care, and optimal outcomes." This 20th anniversary conference had 57 abstracts presenting on older adults based on a search of "geriatrics," "elderly" or "older," however, given the limitation of this type of query, we conducted a manual review of all the presented abstracts. Based on our review, we have summarized the themes observed relevant to the older adult GI oncology population.

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Trends from precision to personalized

The oral abstract presentation on anecaliximab (matrix metalloproteinase 9, MMP9, inhibitor) with FOLFOX6 as first-line treatment in advanced gastric and gastroesophageal cancer (GAMMA-1) was a negative study.¹ However, subgroup analysis showed improved overall survival (OS) of 13.9 months in patients 65+ versus 10.5 months in patients <65 years of age (HR 0.64, $p=0.29$).¹ Dr. Martine Extermann led the discussion after this presentation to explain that the rationale for improved survival in older adults is likely related to the increased expression of MMP9 in older adults. Previously, a mouse model of ischemic stroke showed higher MMP9 activity in older mice compared to younger mice.² This result suggests that tumor biology and aging biology are important factors to consider when designing clinical trials and targeted therapies in older patients. Further, she implored that researchers in precision medicine not only focus on tumor-related factors and biomarkers, but also collect patient-related factors, such as comorbidities, functional status, and nutrition through the use of geriatric assessment (GA). Collecting patient factors could help advance the field in a more patient-centric way when developing novel treatments. Additionally, Williams *et al*, showed that the integration of GA into routine GI consultation is feasible and identified a high prevalence of GA impairments in older adults with GI malignancies when incorporated into the routine clinic work flow.³

Treatment patterns in older adults

Another theme at this year's conference was treatment patterns in older adults. For example, patients with advanced pancreatic cancer were more likely to be treated with FOLFIRINOX if younger (median age 57) versus gemcitabine/nab-paclitaxel if older (median age 66).⁴

Undertreatment

Undertreatment of older adults was one theme observed at the symposium. A Canadian analysis showed that 65% of 71–80 year olds and 89% of 81+ year olds with non-curative pancreatic cancer did not receive cancer-directed therapy.⁵ Older age, especially 80+ years of age, decreased the odds (OR 0.42 and OR 0.14, respectively) of seeing medical oncology to receive treatment for non-curative pancreatic adenocarcinoma, but 81% of patients did see palliative care.⁵ Although all older patients may not be candidates for systemic treatment, medical oncology evaluations may offer additional supportive care in collaborations with palliative care specialists. Further, the addition of GA to routine oncology care can help with decision making for chemotherapy as in ASCO guidelines as well as identify fit patients who are chronologically older and may be candidates for systemic treatments.⁶

Kang *et al* reported that patients 70 and older with rectal cancer were less likely to receive neoadjuvant treatment (25% versus 44%, $p<0.0001$) or adjuvant treatment (29% versus 55%, $p<0.0001$) for rectal cancer compared to younger patients.⁷ Older patients had worse survival (HR 2.9, $p<0.0001$), but there was not a difference in cancer-specific survival or relapse-free survival.⁷

Reduced dose intensity does not affect survival

The utility of adjuvant chemotherapy in stage II colon cancer, especially for older adults is controversial. One group evaluated the Surveillance Epidemiology End Results (SEER) linkage with Medicare claims to explore the patterns of adjuvant chemotherapy and survival in patients with stage II colon cancer.⁸ Fourteen percent received adjuvant therapy, of whom 33% received oxaliplatin.⁸ After adjustment for patient and tumor characteristics, the 3-year survival was not different for patients who received adjuvant chemotherapy versus those who did not.⁸

A Japanese study identified 95 older patients (70+ years) with stage III colon cancer.⁹ In this cohort, 61.1% received adjuvant chemotherapy, of whom 67.2% completed chemotherapy.⁹ Thirty percent had a relapse, with 3-year recurrence rates of 24.3% (completion of chemotherapy) versus 37.8% (not completed), but this was not statistically significant.⁹ N2 disease was the only risk of recurrence (HR 6.95, $p < 0.01$); however, the addition of oxaliplatin was a risk factor for recurrence in older patients (HR 10.4, $p < 0.01$).⁹ The 3-year survival rate was similar in those who completed adjuvant chemotherapy versus those who did not.⁹ This study further emphasized the negative benefit of oxaliplatin in older adults as observed in the MOSAIC study.¹⁰

Further, a Brazilian group studied very old (80+ years of age) patients with colorectal cancer in a single-institution cohort.¹¹ Of the 88 patients with GI cancers, 40 patients had colorectal cancer, of which 47.5% were stage 4 (median OS of 27.9 months).¹¹ In this cohort, 57.7% of patients received chemotherapy, of which the majority received 5-fluorouracil monotherapy.¹¹

Investigators from Fox Chase Cancer Center evaluated gemcitabine/nab-paclitaxel schedules in older adults with metastatic pancreatic cancer.¹² The traditional schedule of Days 1, 8, 15 every 4 weeks was compared to the modified schedule of Days 1, 15 every 4 weeks.¹² Patients with the traditional schedule were more likely to have dose reductions and higher grade 3+ adverse events than the modified schedule.¹² More than half of the patients required an additional dose reduction over the course of treatment.¹² Median OS was not significantly different (traditional 13 months vs modified 11.7 months, $p = 0.1$).¹² However, the sample size was limited, and further investigations are necessary.

Slagter *et al* presented “A comparison of elderly versus nonelderly patients in the CRITICS gastric cancer trial,” a large landmark clinical trial with 172 patients, who were 70 years or older.¹³ Age correlated with decreased relative dose intensity in preoperative chemotherapy, but this did not affect surgical resection rates and complications.¹³ Although older adults were less likely to receive post-operative treatment, older adults were more likely to receive lower doses in the post-operative chemotherapy arm.¹³ Survival was not significantly different in older versus younger patients.¹³

Prognostic factors

The Japanese study by Hasegawa *et al* conducted a “Prognostic factor analysis in the third-line chemotherapy for elderly patients with metastatic gastric cancer.”¹⁴ They reviewed 185

patients who received palliative third-line chemotherapy aged 70 and older.¹⁴ Multivariate analysis found three prognostic factors affecting poor survival with third-line chemotherapy: performance status of 2 (HR 8.89, $p = 0.001$), serum lactic acid dehydrogenase level > 240 IU/l (HR 2.75, $p = 0.002$), and median progression-free survival (PFS) with second-line chemotherapy of < 3 months (HR 1.89, $p = 0.045$).¹⁴ This group developed a prognostic index, dividing patients into low- (0 factor), intermediate- (1–2 risk factors), or high- (3 risk factors) risk groups. Median OS for each group was 12.6, 6.0, and 3.0 months, respectively ($p < 0.001$).¹⁴ Such tools may help us further determine which older patients would benefit from palliative chemotherapy; however, further validation is warranted.

A study from University of Alabama at Birmingham investigated the proportion of older adults with GI malignancies reporting financial distress and characterized GA and cancer-related factors associated with financial distress.¹⁵ Of the 233 patients with the median age of 68, 26% report financial distress.¹⁵ Such patients with financial distress were more likely to be younger, be black race, have low education, have one or more falls, be limited a lot in walking one block, take more than four medications, have more than one comorbid condition, report impaired instrumental activities of daily living (IADL), and have impaired activities of daily living (ADL).¹⁵ Such factors of the GA and demographics may help clinicians identify older patients at increased risk for financial distress.

Tolerability of chemotherapy

Given the limited data in older patients, a three-center retrospective analysis evaluated patients 75+ years of age who received trimodality therapy for esophageal cancer from 2007 to 2013.¹⁶ All patients received neoadjuvant radiation with concomitant chemotherapy followed by esophagectomy.¹⁶ Of 578 patients, 38 (7%) were 75 years or older, of which 87% received 50.4Gy/28 fractions.¹⁶ The most common chemotherapy was 5-fluorouracil with cisplatin (37%), followed by 5-fluorouracil with docetaxel (24%).¹⁶ Thirty-four percent of patients developed acute grade 3 toxicity with chemotherapy: hematological (10%), nausea (8%), esophagitis (5%) and fatigue (5%).¹⁶ Post-operative complications more commonly were respiratory (39%), arrhythmia (32%), anastomotic leak (5%), and ileus (5%).¹⁶ Within 90 days of surgery, two deaths were observed (1 - empyema, 2 - DIC and sepsis).¹⁶ Median OS was 4.4 years and disease free survival 2.3 years, which is similar to younger patients.¹⁶

Further, there are limited treatment data on older adults with advanced pancreatic cancer. A Hispanic-rich cancer center reported on their cohort of 48 patients with advanced pancreatic cancer who were 65 years or older, of which 31% were Hispanic.¹⁷ First-line treatment included FOLFIRINOX ($n=9$), nab-paclitaxel/gemcitabine ($n=11$), gemcitabine ($n=11$), other ($n=9$), and supportive care ($n=2$).¹⁷ In this cohort, survival was lower than historic phase 3 clinical trials with these regimens.¹⁷ Patients receiving two or more agents had higher performance status and albumin at baseline.¹⁷ Most patients had grade 0–2 toxicities, with more neutropenia and nausea/vomiting in combination treatments.¹⁷ Another study in 83 older adults with pancreatic cancer (all stages), who received gemcitabine/nab-paclitaxel, showed the most common grade 3+ adverse events: fatigue (34.9%), neutropenia (27.7%),

and leukopenia (25.3%).¹⁸ Dose reductions were common (83.4%), with either one or both drugs reduced by at least 20%.¹⁸ Survival was similar to historic numbers.¹⁸

Tolerability of radiation

In addition to systemic treatments, tolerability of radiation in older adults was also reported. There are limited concurrent chemoradiation data in older adults with rectal and anal cancer receiving pelvic chemoradiation. NRG Oncology evaluated the adverse events in patients 70+ versus < 70 years of age who had previously enrolled in six NRG trials (RTOG 9811/0012/0247/0529/0822 & NSABP R-04).¹⁹ Although most baseline characteristics were similar, older patients had worse baseline performance status (defined as 1–2) (23% versus 16%, $p < 0.01$).¹⁹ Older patients were less likely to have completed their chemotherapy (78% versus 87%, $p < 0.01$) but had similar median duration of radiation.¹⁹ Older patients were more likely to have grade 3+ gastrointestinal adverse events but less likely to have 3+ skin adverse events.¹⁹

Another study evaluated the outcomes of patients with unresectable/locally recurrent intrahepatic cholangiocarcinoma treated with hypofractionated proton or photon radiation therapy.²⁰ Of the 66 patients in this study, the median age was 76 years, and 41% were 80+ years of age.²⁰ Of the 51 patients treated with definitive intent, the 2-year local control rate was 96%, PFS 35%, and OS 60%.²⁰ Therefore, this treatment may be considered in older adults who are medically inoperable.

Future directions

There is an increasing awareness of the value of studying older adults with GI malignancies. Most analyses of older adults with GI cancers were retrospective in approach, but the general conclusions were that we need more prospective studies in this growing and vulnerable population and should encourage the incorporation of GA into routine care and clinical trials. An example of this is the “Multicenter open-label phase II trial to evaluate nivolumab and ipilimumab for second line therapy in elderly patients with advanced esophageal squamous cell cancer (RAMONA)” that will assess geriatric status with the G8 screening tool and the Deficit Accumulation Frailty Index.²¹ The primary objective is to assess safety as well as quality of life, with examination of time to quality of life deterioration.²¹ They have already enrolled 18 patients as of September 2018 and have also incorporated translational components, such as predictive biomarkers, organoid cultures, and microbiome analysis (NCT034166244).²¹ Further prospective clinical trials incorporating GA and biomarkers are necessary in older adults with GI malignancies, which will allow us to provide evidence-based personalized care to our older patients.

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