Management of the Older Patients with Gastric Cancer

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Gastric cancer is one of the commonest malignancies with high rates of mortality worldwide. Older gastric cancer patients who are fit for trial inclusion may benefit from surgical intervention and peri-operative systemic chemotherapy strategies. For patients with metastatic disease, management has been revolutionized by the use of anti-HER2 directed therapies as well as immune checkpoint inhibitors with or without chemotherapy. Early data suggest that fit older patients may also benefit from these therapeutic interventions. However, once again there may be limitations in extrapolating these data to everyday clinical practice with older patients being less likely to have a good performance status and an intact immune system. Therefore, determining the functional age and not just the chronological age of a patient prior to initiating therapy becomes very important. The functional decline including reduced organ function that may occur in older patients makes the integration of some form of geriatric assessment in routine clinical practice very relevant.

gastric cancer elderly

1. Introduction

Gastric cancer is one of the commonest cancers worldwide. Based on the GLOBOCAN 2020 data, stomach cancer is the sixth most frequent neoplasm and the third most deadly cancer, with an estimated 768,793 deaths [1]. Gastric cancer incidence and mortality are highly variable by region and are dependent on diet and the prevalence of Helicobacter pylori infection. Despite an upward trend in new cases among the young, it is still considered a disease of older individuals [2]. In the UK between 2016 and 2018, approximately 50% of new cases of gastric cancer were diagnosed in people over the age of 75, while the highest rates were in the 85 to 89 age group [3]. In the US, the average age at diagnosis for stomach cancer is 68, with 6 out of 10 people diagnosed being 65 or older [4]. Increasing incidence with age presumably reflects cell DNA damage accumulating over time, resulting from biological processes and known risk factors. In addition, owing to an upsurge of life expectancy, a corresponding increase in gastric cancer cases in elderly individuals is noticed.

2. Genetic and Molecular Characteristics

Over the past few years, great advances have been made towards the molecular characterisation of gastric cancer. Based on the recently described Cancer Genome Atlas (TCGA), the molecular and genetic alterations of gastric cancer can be classified into four distinct types: Epstein Barr Virus—infected tumours, tumours with Microsatellite

Instability (MSI-H), tumours with Chromosomal Instability (CIN) and Genomically Stable (GS) tumours [5]. It is postulated that resected MSI-H gastric tumours may have a better outlook, possibly due to a high burden of tumour-infiltrating lymphocytes and lower rate of lymph node metastasis. In the adjuvant/neo-adjuvant setting, MSI-H phenotype may indicate a favourable prognosis, providing the potential option for omitting peri-operative or adjuvant chemotherapy. In the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, patients with MSI-H tumours who received perioperative chemotherapy had worse median Overall Survival (OS) compared to patients with MSS tumours [6]. On the other hand, in the surgery alone arm, patients with MSI-H phenotype had a much better median OS as compared to the microsatellite-stable patients [7]. In the metastatic setting, very promising results have been reported in patients with MSI-H gastric tumours treated with immunotherapy with ages ranging from 43 to 92 years. [8].

Geriatric Assessment-Identification of Frailty

Some of the key components of successful oncological treatment are the establishment of the patient's performance status and the stratification of risks prior to therapy. However, for older patients, performance status is often not enough to assess fitness for therapy [9]. For these patients, it is vital to integrate tools in everyday clinical practice for the prediction of frailty and the identification of vulnerable individuals prior to considering treatment options [10]. Chronological age alone cannot distinguish frailty, and functional age estimated by using predictive models can be a better prognostic marker for risk stratification. A validated score to assess functional status is the Comprehensive Geriatric Assessment (CGA) [11]. CGA encompasses many aspects, such as physical function, nutrition, mental or psychological status, functional status, social support and geriatric syndromes. CGA is an effective tool for use in older patients receiving chemotherapy, especially in terms of predicting chemotherapy-induced toxicity [12]. Despite the valuable role of GCA, it can be time-consuming and a challenge to resources. Two screening tools recommended by the International Society of Geriatric Oncology (SIOG) are the G-8 and VES-13 [13]. Both are convenient and easy to use, can be reliable in clinical practice and can be completed in a short period of time. Another important factor that should be taken into consideration in these patients is sarcopenia. The prevalence of sarcopenia among patients with gastric cancer has been reported to be as high as 38%. [14]. Sarcopenia is an independent prognostic factor for severe complications after gastrectomy [15].

3. Localised Gastric Cancer

Surgical Management

Considerable improvements in the surgical management of gastric cancer have been achieved over the last two decades. Improvements in endoscopic techniques allowing for early detection of cancer, better anaesthesiologic and minimal surgical procedures all create a better scope for the surgical management of older patients with gastric cancer.

Endoscopic Submucosal Dissection (ESD) is the treatment of choice for early gastric cancers that are well-differentiated, non-ulcerated, less than 2 centimetres and clearly confined to the mucosa (T1a) [16]. The incidence

of nodal metastasis is negligible. ESD can be a safe treatment option in frail older patients, even in the presence of severe comorbidities. According to the Japanese guidelines, older patients with severe comorbidities and high operative risk for gastrectomy who do not completely fulfil the indications for ESD, can still be considered for the procedure [17]. Kakushima et al. demonstrated that older patients with co-existing medical problems who had an R0 resection did not have a statistically significant higher complication rate compared to younger patients [18]. With regards to adverse events, the most commonly reported complications were perforation, post-operative bleeding and rarely postoperative pneumonia [19].

For cancers staged IB-III, surgery is necessary for potentially achieving cure. However, many surgeons are reluctant to proceed with gastrectomy in older patients due to a high burden of comorbidities, elevated perioperative risk and post-surgical complications. In the past, only a very low percentage of patients over 60 years underwent any form of surgical intervention. In England, data collected over a 25-year period (1957–1981) revealed that only 13% of patients over 80 years received any systemic treatment and less than 20% had undergone surgery [20]. However, over the last 20 years reported resection rates have increased substantially for this patient group [21]. Despite innovations in surgical techniques, the prognosis of older patients remains poorer compared to younger ones. Many surgeons are reluctant to proceed with D2 lymphadenectomy in octogenarians in view of a high prevalence of perioperative complications.

4. Perioperative (Neoadjuvant) Treatments

Recurrent metastatic disease is still the main cause of death from GC. Hence, increasing the R0 resection rate and reducing recurrence and metastasis are some of the main goals of gastric cancer management. Perioperative chemotherapy is recommended for gastric cancers staged IB or higher [16]. In most European countries, the preferred regimen for use in the peri-operative setting in fit patients is a combination regimen of 5-Fluororuracil, Leucovorin, Oxaliplatin, Taxotere (FLOT) [22].

Postoperative (Adjuvant) Treatment

Postoperative adjuvant therapy may be considered for patients with ≥Stage IB gastric cancer and prior surgery who did not receive pre-operative chemotherapy [16]. In Asian countries, adjuvant treatment is more likely to be given after surgery and D2 lymph node dissection in patients with stage II/III gastric cancer [17]. In contrast, in North America chemoradiotherapy is a popular adjuvant treatment option.

5. Metastatic Gastric Cancer

5.1. Systemic Therapy

A substantial proportion of patients diagnosed with gastric cancer present with metastatic disease. Japanese and European guidelines [16][17] suggest that fit patients with good performance status and a low burden of comorbidities can benefit from systemic chemotherapy. Treatment typically comprises doublets or triplets

containing platinum and a fluoropyrimidine with or without a taxane. The FLOT65+ study which included 143 patients with measurable locally advanced or metastatic adenocarcinoma with a median age of 70 years showed lack of benefit for the triplet (FLOT) over the doublet (FLO) combination [22]. No differences were detected for patients over 70 years in relation to Progression Free Survival (PFS) and OS. The triple combination was associated with more treatment-related grade 3/4 adverse events (FLOT, 81.9%; FLO, 38.6%; $p < 0.001$) and significant deterioration of quality of life.

In the SPIRITS phase III trial, monotherapy with S-1 was compared to S-1 plus Cisplatin, a first-line regimen commonly used in Asian countries. The median age was 62 years, and benefit in terms of OS was noted for the combination of S-1 plus Cisplatin for patients younger than 60 years. A subgroup analysis did not report any relation to toxicity with age, but more grade 3/4 adverse events including leukopenia, neutropenia, anaemia, nausea and anorexia, were observed for the combination chemotherapy group [23].

5.2. Targeted Agents and Immunotherapy

The monoclonal antibody trastuzumab is used in advanced or metastatic gastric cancer in combination with conventional chemotherapy in the first line setting. The ToGa trial has demonstrated a survival benefit for the use of trastuzumab when used in combination with chemotherapy [24].

Ramucirumab, a fully humanised monoclonal antibody against VEGFR2, can be used in patients who have failed first line therapy for metastatic gastric cancer [25]. When used in older patients, ramucirumab appears to have a tolerable safety profile. In a subgroup analysis of the REGARD trial, patients over 65 years seemed to benefit in terms of PFS and OS as compared to placebo to a similar extent as those under Immune Checkpoint Inhibitors (ICI) have shown promising efficacy in the setting of advanced or metastatic gastric cancer; however, there is very little available evidence for the use of ICI in frail patients with a poor performance status (≥2). Theoretically, ‘immunosenescence’, the decline in the immune system occurring with older age, can reduce the efficacy of immunotherapy [26].

The ATTRACTION-2 trial, a randomised double blind phase III trial, assessed the use of nivolumab in pre-treated patients with advanced gastric or gastroesophageal junction cancer. Subgroup analysis for patients over 65 years tended to show a benefit in terms of OS with nivolumab compared to placebo [27]. The KEYNOTE-590 trial investigated the addition of pembrolizumab to chemotherapy compared to chemotherapy alone as first-line treatment of advanced oesophageal cancer [28]. Patients over the age of 65 appeared to have a benefit in terms of PFS and OS. Older adults with good performance status generally seem to benefit similarly when treated with single-agent immune checkpoint inhibitor (ICI) therapy (i.e., PD-1 or PD-L1) to their younger counterparts [29]. However, while overall toxicity appears similar both across landmark trials and in single-institutional studies, increased hospital admissions because of poor functional status and multimorbidity in everyday clinical practice remain a challenge.

6. Conclusions

Older adults represent a substantial proportion of patients with stomach cancer. Those older patients who are fit enough to be enrolled into clinical trials appear to gain similar benefit from treatment to their younger counterparts. However, physiological heterogeneity, quite often reduced treatment tolerance and different treatment goals make management of such patients in everyday clinical practice very challenging. Some form of baseline geriatric health assessment in the clinic can help predict the likelihood of a good therapeutic effect without unwanted toxicity, and in this way contribute to patients' and clinicians' treatment decisions. Unfortunately, patients who are perhaps more frail are underrepresented in landmark clinical trials, often not reflecting 'real world' circumstances and the true age distribution of the disease. Tailored research in the form of carefully designed 'elderly-specific' trials is needed to address this evidence gap.

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