Cancer Incidence and Chemotherapy-Induced Adverse Effects in Asia

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ABSTRACT

Objective: Primary care givers and researchers are challenged every day in finding an appropriate treatment for cancer. Chemotherapy is one of the treatments to treat cancer, however, the adverse effects from chemotherapy present a significant problem. The aim of this review is to present current standings of the incidence of cancer and the adverse effects from chemotherapy among Asians. **Method**: Studies which were conducted from 1990 through June 2018 containing phrases such as 'Cancer incidence in Asia', 'chemotherapy-induced adverse effects in Asia', 'CIPN in Asia', 'CINV in Asia' and 'chemotherapy -induced anaemia in Asia' were searched through PubMed, Google scholar and Scopus. Where appropriate, 'Asia' was replaced by the name of a specific country to ensure searching of the database. **Results:** Incident rates of new cancer cases and death in Asia are increasing which are estimated to reach 48 % of new cases and 55 % of death. While studies had reported using different chemotherapeutic agents to treat cancer, most of them detailed the adverse effects from chemotherapy that affected the patients, thus affecting their quality of life. **Conclusion:** Findings from this review concluded that cancer incident is increasing which may requires early detection of cancer and optimal treatment. This may aid in the selection of an appropriate chemotherapy regimen with reduced side effects.

KEYWORDS: Cancer; Chemotherapy; Asia; Adverse effects; Peripheral neuropathy.

INTRODUCTION

Scientists and primary care givers are challenged every day in finding an apt treatment for cancer which can significantly influence patients and their caregivers. Other than discovering new drugs in the ever-burgeoning field of pharmacology, they are constantly trying to reduce the increasing incidence of adverse effects from the drugs which are detrimental to the patients' health. Chemotherapy or drugs used to treat cancer include agents such as cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate, paclitaxel or docetaxel (1). Among the most common adverse effects of these chemotherapeutic agents include nausea and vomiting (1,2), anaemia (1,2), hair loss (alopecia) (1,2), fatigue (1-3), chemo-brain (1,2) and peripheral neuropathy (3,4).
Chemo-brain, also known as chemotherapy-induced cognitive dysfunction refers to cognitive impairment which is caused by chemotherapeutic agents (5). In a study conducted in 2011 by Argyiou et al. (6), chemotherapy-induced cognitive impairment (CICI) was defined as "the impairment of patients' memory, learning, concentration, reasoning, executive function, attention, and visuospatial skills during and after discontinuation of chemotherapy". Almost 70% of patients with cancer, who receive chemotherapy, experienced cognitive impairment (7-9). Similarly, 18-70% of breast cancer patients have reported loss of cognition soon after initiating chemotherapy treatment (10, 11).
Peripheral neuropathy refers to a condition resulting from damage from chemotherapeutic agents on peripheral nerves which are distant from the brain and spinal cord also known as chemotherapy-induced peripheral neuropathy (CIPN) (3, 4) The damage caused by the chemotherapeutic agents depends on the degree of toxicity of the agents, the type and dose of the drugs, and the administration time (12). Seretny et al. (13) reported that "CIPN prevalence was 68.1% (57.7–78.4) when measured in the first month after chemotherapy". 50% of those with CIPN have pain, 25% of these patients reported experiencing severe pain (14). The severity of CIPN depends on the accumulation of the dose with symptoms arising either during or upon cessation of the chemotherapy treatment (15). In Asia, there is a few information on the incidence of cancer and the chemotherapeutic-induced adverse effect. The aim of this review is to appraise the available information on the incidence of cancer and the chemotherapy induced adverse effects among Asians.

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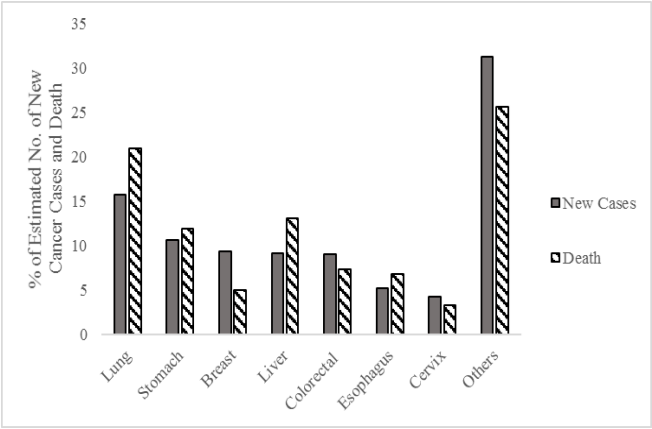
INCIDENCE OF CANCER IN ASIA

Asia is the largest continent in the ecosphere with a current population of 4.55 billion which makes up to 60% of the world population (16) and by 2030, this figure has been projected to increase to a staggering 4.90 billion (17). China and India alone account for 37% of the worldwide population. (18).
This continent has reported about 44% of all cancer cases and more than half of all cancer deaths in the world, China being the most over-populous nation in the world, naturally contributes half of cancer prevalence in this part of the world (19). While the USA has reported 153 deaths per 100,000 cases; Korea, Singapore, China, and Japan combined have mortality rates between 154 and 180 deaths per 100,000 cases except Mongolia which reported a higher than any other Asian country rate among male (204 deaths per 100,000). Mongolia yielded the highest mortality rate amongst women with 136 deaths per 100,000 population; followed by the Philippines and Singapore (124 and 109 deaths per 100,000 population respectively) (18). Rather when compared to the USA which has a higher population of women but accounted for only 112 deaths per 100,000 population (18).
Ferlay et al. (20) reported that the estimated new cancer cases in Asia is 48 % (6.77 million new cases) and the death rate is 54.9 % (4.50 million death). The highest cancer prevalence types among Asian women were breast, lung, and cervical cancers. However, in men they were lung, stomach, and liver cancers. The highest death rates caused by cancer in women are lung and breast, while in men are lung, and stomach (18, 21). Lung cancer has the highest estimated new cancer cases and death rates in both male and female, followed by stomach, liver and breast as shown in Fig. 1 (19).

Fig 1: Total estimated new cases and death for both genders according to carcinoma in situ. It shows that lung cancer has the highest estimated new cases and death followed by stomach, liver and breast. Source the Cancer Atlas [19] with modifications.



Cancer health care services which are responsible to diagnose and treat cancer patients, are still inefficient when it comes to the low and middle-income countries within the Asia continent. Poor cancer health care services are unable to prevent, diagnose, treat, and follow up with the rising demand of new cancer cases within Asia. Cancer of the breast, lung, and colorectal among women appear elevated in high human development Index (HDI) countries. Whereas medium HDI countries seem to yield cancers of the oesophagus, stomach, and liver. Cervical cancer is prevalent in low HDI countries (22). Youlden et al. (23) reported that escalation in mortality rates of breast cancer occurred in many countries especially in Malaysia and Thailand, whereas these rates are stabilizing high in Hong Kong and Singapore. In high-income countries, the reasons which suggest higher rates of breast, colorectal and thyroid cancers are attributable to the adaptation to the western lifestyle (23). Primary care givers were able to detect early stages of cancer with the use of computerized tomography (CT) scan, endoscopy, and ultrasound scanning techniques which were not readily available in low and middle-income countries in Asia (22, 24-25).

High-income countries such as Singapore, Japan, and South Korea have advanced cancer care, whereas Bangladesh, Cambodia, China and other low-income countries have more rudimentary cancer care services to offer. Even though higher-middle-income countries such as Malaysia, Thailand, and China have better cancer care services than the low-income countries, they have yet to reach an acceptable level of standard cancer care by international standards (26). Table 1 depicts the status of cancer health care services according to income category within the countries in Asia (26).

Table 1: Cancer health services according to income category in Asia. Source: Sankaranarayanan et al 2014 926)

Income Category	Cancer health services
Low-income	Poorly developed, low human resources, inadequately support by governments
Lower-middle-income	Health systems are fragmented, mainly in urban areas.
Higher-middle-income	The health systems are still evolving; a potential for further improvements. Rural areas have inadequate services in large countries such as China.
High-income	High government investment, organised, state-of-the-art diagnostic and treatment services within public health services.

The patients' biological systems which have been affected by the adverse effects from chemotherapy are succinctly explained accordingly.

CHEMOTHERAPY-INDUCED ADVERSE EFFECTS ON THE NERVOUS SYSTEM

Central Nervous System: Chemotherapy-Induced Cognitive Impairment (CICI)

CICI or Chemo-brain as discussed earlier is a term used to describe one of the adverse effects caused by chemotherapeutic agents. In recent years, more research has focused on the correlation between chemotherapy and cognitive impairment. However, while the incidence is increasing, there are relatively few studies which examine cognitive impairment among patients in Asia. Moon et al. (27) reported that breast cancer patients in South Korea with co-morbid mood disturbance were likely to experience reductions in perceived cognitive function. These patients were treated with cyclophosphamide, doxorubicin, paclitaxel and docetaxel. Another clinical trial revealed that cognitive deficits were found in chemotherapy-treated Korean women with moderate to large effect sizes when compared with the control group, these patients had localized breast cancer and were treated with a combination of cyclophosphamide, doxorubicin or epirubicin, 5-fluorouracil, and paclitaxel or docetaxel (28).

In Singapore, Cheung et al. (29) reported that most patients experienced cognitive changes and symptoms got worse upon cessation of their anthracycline-based chemotherapy including combination of doxorubicin and cyclophosphamide or combination of FEC (5-flurouracil, epirubicin and cyclophosphamide) within one year. The patients also noticed that numbness (peripheral neuropathy) had overshadowed the cognitive impairment.

In Malaysia, a survey which involved 90 patients with ovarian uterine, cervical or breast cancers who were given chemotherapy regimens which included paclitaxel, carboplatin, gemcitabine and doxorubicin showed that 43.3% of patients experienced confusion or loss of concentration and suffered from sadness or depression (30). Cheung et al. (31) conducted a cross-sectional survey among oncology practitioners from Singapore and Thailand which showed that cognitive impairment was found in patients, with memory (77.1 %) and concentration (74.6 %) being particularly problematic.

These results are in line with different studies performed in the West. Vardy et al. (32), reported that patients with colorectal cancer from Toronto, Canada (n=235), and from Sydney, Australia (n=127) who received fluorouracil, oxaliplatin or capecitabine had more cognitive impairment when compared to the healthy controls. Another study, conducted in the USA, found that 65% of 42 patients with breast cancer who received FDC or paclitaxel had cognition impairment (33). From the above findings, the most likely chemotherapy drugs which may cause cognitive impairment are cyclophosphamide, doxorubicin, paclitaxel, docetaxel, or 5-flurouracil.

Peripheral Nervous System: Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Another side effect of chemotherapeutic agents is the chemotherapy-induced peripheral neuropathy (CIPN). CIPN generally affects distal sites first, but with cumulative doses, the symptoms increase in severity causing damage to proximal nerves. Sensory nerves damage can occur before motor nerves (34). Park et al. (35), reported peripheral neuropathy of different chemotherapeutic agents as shown in Table 2. The study reported large sensory fibres are mainly affected, while smaller sensory nerves are rarely damaged with certain anticancer drugs. The findings from the study also suggests that sensory nerve damage is more common than motor damage.

The severity of CIPN has been reported to directly correlate to the cumulative dosage, number of treatment cycles, and also the co-administration of different neurotoxic anticancer agents (36). To further strengthen the effect of co-administration of neurotoxic anticancer agents on the severity of CIPN, it was shown that, the frequency of neuropathic symptoms when cisplatin alone was used was almost 50%, while the symptoms reached 90 to 100% in women receiving the combination of cisplatin and paclitaxel for ovarian cancer (37). Please refer Table 2.

As for chemo-brain, very few studies examined CIPN in Asia. One of these studies, conducted in Korea by Hye et al. (38), found that 141 patients who received taxanes and platinum to treat cancer experienced moderate levels of CIPN. Whereby, 70% had experienced tingling sensation in the feet and nerve pain with high cumulative doses of these drugs. These symptoms increased substantially and became more pronounced with cumulative doses of chemotherapeutic agents. Another study also in Korea, found that levels of CIPN, in 130 patients treated for gynaecologic cancer, adversely affected their quality of life and daily activities (39).

In Pakistan, Bano et al. (40) surveyed 45 patients who had colorectal cancer and were treated with FOL-Folinic acid, F-Fluorouracil (5-FU), and OX-Oxaliplatin (FOLFOX) suffered peripheral neuropathy with different grades of toxicity. The degree of severity of CIPN was also assessed at the completion of the chemotherapy and was graded on a scale between 0 and 5, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (41).

In Japan, a study by Kanbayashi et al. (42) found that 35% of patients treated with paclitaxel or a combination of paclitaxel with capecitabine, carboplatin or nedaplatin had grade 1 and that 29% of the patients had grade 2 peripheral neuropathy. On the contrary, another study by the same group Kanbayashi et al. (43) showed less neuropathy with taxanes, but more with Oxaliplatin (31%) and Vincristine (29%) grade 2 as presented in Table 3. In Thailand, a study by Wutthikonsammakit et al. (44) showed neurotoxicity occurred in all patients. Furthermore, the numbers of patients experiencing grade 1, 2 and 3 neurotoxicity increased with the increasing cycle of oxaliplatin.

(*refer Table 3*).

Drug	Threshold Dose	Sensory Neuropathy	Motor Neuropathy
Paclitaxel	>300 mg/m2	Mainly	Higher doses
Docetaxel	>100 mg/m2	Mainly	Higher doses
Oxaliplatin	>550 mg/m2	Mainly sensory neuropathy with acute symptoms.	Acute cramps fasciculation
Cisplatin	>350 mg/m2	Mainly	Rare
Vincristine	>2-6 mg/m2	Mainly	Muscle cramps, low distal weakness
Thalido-mide	>20 g	Mainly	Muscle cramps, low distal weakness
Bortezomib	>16 mg/m2	Small-fibre sensory neuropa-thy	Rare

Table 2: Some of peripheral neuropathy caused by anticancer drugs. Source: from Park et al. 2013 (35)

CTCAE v3.0 grades	Borte-zomib	Taxanes	Oxaliplatin	Vincristine
0 = normal	**10**	**48**	**26**	**31**
1=asymptomatic, loss of deep tendon reflexes	**5**	**2**	**8**	**3**
2=moderate symptoms	**6**	**4**	**16**	**15**
3= severe symptoms	**7**	**4**	**2**	**3**
4= life-threatening consequences	**0**	**0**	**0**	**0**
5= death	**0**	**0**	**0**	**0**

Table 3: Sensory peripheral neuropathy grades. Source: from Kanbayashi et al. 2013 (42)

CHEMOTHERAPY-INDUCED ADVERSE EFFECTS ON HAEMATOLOGIC SYSTEM

Chemotherapy-induced anaemia (CIA) is one of the most common side effects caused by anti-cancer drugs. Tanaka et al. (45) conducted a questionnaire-based survey on CIA in Japan and found that 42,920 (40 %) from 106,690 patients with 8 different types of cancer and who had been subjected to different kinds of chemotherapy had CIA. The study revealed that when compared to studies from the USA, the estimated volume of blood transfusions to patients with CIA in the United States was about 7 times greater than that in Japan.
In addition, in another study carried out in Japan, Chou et al (46) reported that 63% of patients with multiple myeloma (n=34) had Grade 4 neutropenia more often with chemotherapy treatment of VAD (vincristine, doxorubicin and dexamethasone) than with MP (melphalan and prednisone). Another study in Japan was conducted on 85 patients with head and neck cancer who were treated with TPF (docetaxel, cisplatin, and fluorouracil), DC (docetaxel and carboplatin) or other regimens. The study found that neutropenia occurred in 70% of patients who were treated with TPF compared to 77% of those with DC (47). Shiota et al. (48) examined the adverse effects of chemotherapy among 37 Japanese men who had castration-resistant prostate cancer and treated with docetaxel for 3 to 4 weeks. The findings from the study reported that 97.3% of the patients had neutrocytopenia, 64.9% had leukopenia, 27.0% had lymphopenia, and 10.8% of the patients had febrile neutropenia (FN). In another study which was also performed in Japan, Shiozawa et al. (49) reported several findings of severe adverse effects from 13,935 patients who had squamous cell carcinoma of the skin, lung cancer, breast cancer, colorectal cancer, gastric cancer, ovarian cancer, cervical cancer and malignant lymphoma, they were treated with irinotecan on different regimen. The findings from the study suggested that 34.8% had grade 3 and 4 leukopenia, and 12.4% had thrombocytopenia.

In Korea, Kim et al. (50) examined the adverse effects from chemotherapy in 610 patients with breast cancer who received adjuvant chemotherapy, containing doxorubicin and cyclophosphamide followed by either paclitaxel or docetaxel. The study discovered 44.6% had neutropenia and 8.5% had FN. However, Lin et al. (51) reported 13% of 353 women with breast cancer in Taiwan had neutropenia and FN. Those patients were treated with different regimes of doxorubicin, docetaxel, paclitaxel, cyclophosphamide, or fluorouracil. In Singapore, Chan et al. (52) reported that 13.8% of 189 patients with breast cancer treated with doxorubicin and cyclophosphamide, had FN.

In Malaysia, Wijayahadi et al. (53) examined the effect of FEC and FDC (5-fluorouracil, doxorubicin, cyclophosphamide) regimens on the

immune system of patients with primary malignant breast tumours. The study suggested that all patients in both groups had myelosuppressive side effects, increased monocytes, decreased polymorphonuclear cells and lymphocytes, and significant suppressive of the polymorphonuclear cells phagocytic and killing ability. Another study in Malaysia was conducted by Phua et al. (54) who investigated the chemotherapy adverse effects on 622 patients with breast cancer who were subjected to chemotherapy regimens of either FEC followed by docetaxel, or AC (adriamycin and cyclophosphamide) followed by paclitaxel, or docetaxel, adriamycin, and cyclophosphamide, or docetaxel and cyclophosphamide. The study found that 10% of these patients experienced FN. In South India, Rajendranath et al. (55) reported the outcome of high risk FN in 66 patients with acute leukaemia who were subjected to intensive chemotherapy.

Dattani et al. (56) compared the incidence of neutropenia and neutropenic sepsis among Asian and Caucasian patients. The research surveyed 15 Asian and 15 Caucasian with different types of cancer and who were treated with different combination of chemotherapy but the most common regime was FEC with or without docetaxel. The outcome of the study suggested that 33.3% of Asian and 20% of Caucasian had grade 4 neutropenia, and 20% of Asian and 6.7% of Caucasian had neutropenic sepsis. The research further suggested that more Asian patients developed grade 2 neutropenia compared to their Caucasian counterparts (66.7% vs. 33.3%).

CHEMOTHERAPY-INDUCED ADVERSE EFFECTS ON THE DIGESTIVE SYSTEM

One of the most distressing and common effects of anti-cancer drugs is the chemotherapy-induced nausea and vomiting (CINV). CINV is believed to affect 70–80% of cancer patients despite the administration of anti-emetic agents (57).

Hesketh et al. (58) classified the chemotherapy agents into four groups: highly emetogenic chemotherapy (HEC) (cisplatin ▫50 mg/m2, cyclophosphamide >750 mg/m2, carboplatin, doxorubicin >60 mg/m2, and methotrexate >1000 mg/m2), moderate emetogenic chemotherapy (MEC) (cisplatin <50 mg/m2, cyclophosphamide <750 mg/m2, doxorubicin 20–60 mg/m2, epirubicin <90 mg/m2, and methotrexate 250–1000 mg/m2), low emetogenic chemotherapy (LEC) (docetaxel, 5-fluorouracil <1000 mg/m2, methotrexate <250 mg/m2, and paclitaxel), and no emetogenic chemotherapy (methotrexate ▫50 mg/m2, vinblastine, vincristine, and vinorelbine).

In Taiwan, Liau et al. (59) examined the CINV in 107 patients with breast and as well as head and neck cancer who were treated with either HEC or MEC regimen. The findings from the study reported that 64.3 % had experienced vomiting and 59.5% nausea when the patients were treated with HEC, while 73.9% had experienced vomiting and 55.4% nausea when they were treated with MEC. Kim et al. (60) studied the CINV in 648 patients with cancer from five Asian countries (China, India, Taiwan, Korea, and Singapore) who were treated with either HEC or MEC. They found that the incidence of CINV among patients with CINV in prior cycle was 51.9% in cycle 2 and 52.2% in cycle 3, while those who did not have CINV in prior cycle was 8.2% and 4.7% respectively.

In Malaysia, Chan and Ismail (61) looked at chemotherapy adverse effects of 90 patients with ovarian, uterine, cervical, and breast cancers who were treated with chemotherapy regimen of paclitaxel and carboplatin, gemcitabine or doxorubicin. The study revealed that 83.3% had experienced nausea and 78.9% vomiting. Perwitasari, et al. (62) reported that in Indonesia, 74.9% of 179 patients had delayed emesis within 5 days upon receiving chemotherapy. The patients had cervical, ovarian, uterine, or vulva cancer and were treated with cisplatin alone or in combination with one or more of cyclophosphamide, doxorubicin, and 5-fluorouracil.

A different study, conducted by Bourdeanu et al. (63), compared the CINV in 358 women with breast cancer who were treated with a combination of doxorubicin and cyclophosphamide with or without docetaxel in California, USA; the women were from different ethnic origin (Asian, Caucasians, Hispanics, and African Americans), they found that the Asian patients experienced significantly higher levels of CINV compared to non-Asian patients (40% and 22% respectively).

CHEMOTHERAPY-INDUCED ADVERSE EFFECTS ON THE REPRODUCTIVE SYSTEM

Amenorrhea is a long-term chemotherapy-induced adverse effect which may complement other symptoms such as menopause, infertility, and even osteoporosis (64). In China, Zhou et al. (65) determined chemotherapy-induced amenorrhea in 186 premenopausal patients with breast cancer who were treated with epirubicin and taxane based chemotherapy. The study revealed that 43.64% had amenorrhea, and that the rate of chemotherapy-induced amenorrhea in leukopenia group was higher than in the normal group (52.56% and 34.62% respectively). Another study was performed among 286 young Chinese breast cancer patients who were being treated with different combinations of doxorubicin and cyclophosphamide, cyclophosphamide, methotrexate, and fluorouracil or paclitaxel. The findings showed that almost all (91%) of the patients experienced chemotherapy-induced amenorrhea and almost half (49%) experienced chemotherapy-induced menopause of which 61% of them reported to have onset menopause (66). In Malaysia, Tiong et al. (67) reported the incidence of chemotherapy-induced ovarian failure (CIOF) and reversible amenorrhea among 102 premenopausal breast cancer patients who were treated with FEC, FEC followed by docetaxel, or docetaxel followed by cyclophosphamide. The study revealed 93.1% had chemotherapy-induced amenorrhea upon cessation of chemotherapy, and that CIOF increased from 57% at <35 years to 97.9% at >50 years, whereas reversible amenorrhea was reduced from 50% to 14.9 %.

MISCELLANEOUS ADVERSE EFFECTS

In Malaysia, Chan and Ismail 2014 [61] reported that 64.4% of the 90 patients had chemotherapy-induced alopecia, 73.3% experienced dry mouth or thirst, 56.7% felt tired or weak, 56.7% suffered from loss of appetite and 56.7% felt cold. Choi et al. (68) determined chemotherapy-induced alopecia in Korea on 168 patients with breast cancer and reported that 77.8% of the patients experienced moderate to severe alopecia.

Ra et al. (69) looked at chemotherapy-induced dermatological toxicities in Korea, who examined 73 patients with colorectal cancer, gastric cancer,

renal cell cancer or other types of cancer being treated with cisplatin, irinotecan, taxane, fluoropyrimidine, or oxaliplatin. The outcome of the study revealed that 65.8% had at least grade 1 skin toxicity, 38.4% experienced hair loss and 26.0% was subjected to hyperpigmentation.

Yamada, et al. (70) surveyed ocular complications caused by S-1 anti-cancer drug which is an orally active chemotherapeutics agent containing tegafur (a prodrug of 5-fluorouracil), gimeracil, and oteracil (71). A total of 39 patients with stomach, breast, colon, pancreas, lung, or mandibular cancer and who were treated with S-1 anti-cancer drug were asked to complete a survey questionnaire. The outcome of the study suggested that older patients were at a higher risk of developing S-1-related ocular complications (70).

CONCLUSION

Despite Asia being the largest continent in the world, contributing up to 60% of the world's population, cancer mortality and incidence continues to increase over time compared to the rest of the world. Incident rates of new cancer cases and death in Asia are increasing which are estimated to reach approximately 48 % of new cases and 55 % of death. Lung cancer has the highest estimated new cancer cases and death rates in both male and female, followed by stomach, liver and breast. All patients undergoing cancer chemotherapy experience side effects to some degree with an increasing incidence, yet very few studies in Asia have looked at the adverse effects such as CICI, CIPN, nausea and vomiting in these patients. Furthermore, there also appear to be inadequate strategies to treat and manage adverse effects among patients in this part of the world. This is likely due to the fact that most of the advanced cancer care centres are confined to more the developed countries within the continent.

Early detection and careful selection of the most effective treatment is critical in these patients to reduce mortality rate but also to minimise rates of adverse events. This review illustrates the dearth of studies in Asia looking at the incidence of adverse events, showing that further research is required to fully assess the impact of side effects on patients' health while undergoing cancer chemotherapy.

REFERENCES

1. Fleishman SB (2017) Understanding and managing Chemotherapy Side effects, Cancer Care® National office https://media.cancercare.org/publications/original/24-ccc_chemo_side_effects.pdf. Accessed 20 July 2018.
2. The American Cancer Society medical and editorial content team (2016) Chemotherapy Side Effects, American Cancer Society Inc. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html Accessed 20 July 2018.
3. Pachman DR, Barton DL, Swetz M, and Loprinzi CL (2002) Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain, J Clin Oncol 30(30): 3687-96.
4. American Cancer Society (2016) Peripheral Neuropathy Caused by Chemotherapy (printable version), American Cancer Society, Inc https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/peripheral-neuropathy.html. Accessed 23 July 2018.
5. Mayo Clinic Staff (2016) Chemo brain definition - diseases and conditions, Mayo Foundation for Medical Education and Research. http://www.mayoclinic.org/diseases-conditions/chemo-brain/home/ovc-20170224. Accessed 20 July 2018.
6. Argyriou AA, Assimakopoulos K, Iconomou G, Giannakopoulou F, and Kalofonos HP (2011) Either called "Chemo Brain" or "Chemo Fog," the long-term chemotherapy induced cognitive decline in cancer survivors is real. J Pain Symptom Manage 41 (1):126-139.
7. Ahles TA, and Saykin AJ (2007) Candidate mechanisms for chemotherapy induced cognitive changes. Nat Rev Cancer 7: 192–201.
8. Vardy J, Rourke S, Tannock IF (2007) Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 25: 2455–63.
9. Van Dam FS, Schagen SB, Muller MJ, Boogerd W, Wall EVD, Droogleever Fortuyn ME, Rodenhuis S (1998) Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 90: 210–18.
10. Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. (1996) What do cancer patients mean when they complain of concentration and memory problems? Br J Cancer. 74 (10):1674–1679.
11. Ahles TA, Root JC, and Ryan EL (2012) Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. J Clin Oncol. 30(30):3675–3686.
12. Driessen CML, de Kleine-Bolt KME, Vingerhoets AJJM, Mols F, Vreugdenhil G (2012) Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients. Support Care Cancer 20 (4):877-81.
13. Seretnya M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain 155(12):2461-70.
14. Cavaletti G, Cornblath DR, Merkies ISJ, Postma TJ, Rossi E, Frigeni B, Alberti P, Bruna J, Velasco R, Argyriou AA, Kalofonos HP, Psimaras D, Ricard D, Pace A, Galiè E, Briani C, Dalla Torre C, Faber CG, Lalisang RI, Boogerd W, Brandsma D, Koeppen S, Hense J, Storey D, Kerrigan S, Schenone A, Fabbri S, Valsecchi MG, the CI-PeriNomS Group (2013) The chemotherapy-induced peripheral neuropathy outcome measures

standardization study: from consensus to the first validity and reliability findings. Ann Oncol 24: 454-462.

15. Flatters SJL, Bennett GJ (2004) Ethosuximide reverses paclitaxel- and vincristine-induced painful peripheral neuropathy. Pain 109: 150-61.

16. Worldometers (2017) Current World Population, http:// www.worldometers.info/world-population/asia-population Accessed 20 July 2018.

17. Population Reference Bureau (2016) World Population Data Sheet. Population Reference Bureau. https://assets.prb.org/pdf16/prb-wpds2016-web-2016.pdf Accessed 29 July 2018.

18. P f i z e r Facts (2008) The Burden of Cancer in Asia, Pfizer Inc. https:// www.pfizer.com/files/products/cancer_in_asia.pdf Accessed 20 July 2018.

19. American Cancer Society Inc. (2015) The Cancer Atlas, Second Edition. The International Agency for Research on Cancer, and the Union for International Cancer Control http:// canceratlas.cancer.org/assets/uploads/2014/10/19_SoutheastAsia_rev3.pdf Accessed 20 July 2018.

20. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5): E359-86

21. IARC (2012) Globocan Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, IARC International Agency for Research on Cancer http:// globocan.iarc.fr/Pages/fact_sheets_cancer.aspx Accessed 20 March 2018.

22. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012) Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol 13:790–801.

23. Youlden DR, Cramb SM, Har Yip C, Baade PD (2014) Incidence and mortality of female breast cancer in the Asia-Pacific region, Cancer Biol Med 11:101-115

24. Parkin DM, Whelan SL, Ferlay J, Teppo L and Thomas DB (2005) Cancer Incidence in Five Continents Volumes I to VIII. IARC Cancer Base No. 7. International Agency for Research on Cancer https:// www.iarc.fr/en/publications/pdfs-online/epi/sp155/CI5V8.pdf Accessed 28 July 2018.

25. Jemal A, Center MM, DeSantis C, and Ward EM (2010) Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19:1893 –1907.

26. Sankaranarayanan R, Ramadas K and Qiao Y (2014) Managing the changing burden of cancer in Asia. BMC Medicine 12(1), 3.

27. Moon S, Kim SH, Kim MJ (2011) Perceived cognitive function and related factors in Korean women with breast cancer. Asian Nurs Rec 5 (2); 141-150.

28. Jung SM, Cimprich B (2014) Cognitive deficits in Korean women treated with chemotherapy for breast cancer. Cancer Nurs 37(3): E31-42.

29. Cheung YT, Shwe M, Tan YP, Fan G, Ng R and Chan A (2012) Cognitive changes in multiethnic Asian breast cancer patient: a focus group study. Annals of Oncology. 23: 2547–2552.

30. Chan HK, Ismail S (2014) Side Effects of Chemotherapy among Cancer Patients in a Malaysian General Hospital: Experiences, Perceptions and Informational Needs from Clinical Pharmacists. Asian Pac J Cancer Prev. 15 (13), 5305-5309

31. Ting Y, Maung C, Earl S, Jie H, Wai T, Chui K, Ng R, Chan A (2013) Acknowledging the relevance of cognitive changes in cancer patients: perspectives of oncology practitioners in Asia. J Cancer Surviv 7:146-54

32. Vardy JL, Dhillon HM, Pond GR, Rourke SB, Bekele T, Renton C, Dodd A, Zhang H, Beale P, Clarke S, and Tannock IF (2015) Cognitive Function in Patients with Colorectal Cancer Who Do and Do Not Receive Chemotherapy: A Prospective, Longitudinal, Controlled Study. J Clin Oncol 33(34):4085-92.

33. Wefel JS, Saleeba AG, Buzdar AU, and Meyers CA (2010) Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer 116 (14):3348-56

34. Van Gerven JMA, Moll JWB, van den Bent MJ, Bontenbal M, van der Burg MEL, Verweij J and Vecht CJ. (1994) Paclitaxel (Taxol) induces cumulative mild neurotoxicity. Eur J Cancer. 30 A (8):1074-1077.

35. Park SB, Goldstein D, Krishnan AV, Lin CSY, Friedlander ML, Cassidy J, Koltzenburg M, Kiernan MC. (2013) Chemotherapy-Induced Peripheral Neurotoxicity: A Critical Analysis. CA Cancer J Clin. 63:419–437.

36. Kanbayashia Y, Hosokawa T, Okamotog K, Konishid H, Otsujie E, Yoshikawad T, Takagi T, and Taniwakif M (2010) Statistical identification of predictors for peripheral neuropathy associated with administration of bortezomib, taxanes, oxaliplatin or vincristine using ordered logistic regression analysis. Anticancer Drugs. 21(9):877-81.

37. Aurélia D, Simão D, Murad M, Martins C, Cristina V, Karine F, Captein M, and Teixeira AL (2015) Chemotherapy-induced peripheral neuropathy: review for clinical practice, Rev Dor. São Paulo. 16(3):215-20

38. Jeong Hye K, Kyoung Min L, Mi Jin J, Mi Ee S, Soon Haeng L, JeongYun P (2013) Symptom and Interference of Activities of Daily Living of Chemotherapy-Induced Peripheral Neuropathy in Patients Receiving Taxanes and Platinums, Asian Oncol Nurs. 13(3), 145-151.

39. Jeong JH, Nho JH, Kim GS, Lee YE, Yu SY, Lee HJ, Sim YM, and Lee YS (2013) Characteristics and Quality of Life in Gynaecologic Cancer Patients with Chemotherapy-induced

Peripheral Neuropathy. Korean J Women Health Nurs. 19(4):201-210.

40. Bano N, Najam R, and Mateen A (2013) Neurological adverse effects in patients of advanced colorectal carcinoma treated with different schedules of FOLFOX. Chemother. Res. Pract. Article ID 379870, 7 pages.

41. Cancer Therapy Evaluation Program, National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf Accessed 20 July 2018.

42. Kanbayashi Y, Hosokawa T, Kitawaki J and Taguchi T (2013) Statistical Identification of Predictors for Paclitaxel-induced Peripheral Neuropathy in Patients with Breast or Gynaecological Cancer, Anticancer Research. 33: 1153-1156.

43. Kanbayashi Y and Hosokawa T (2012) Predictors of Chemotherapy-Induced Peripheral Neuropathy, Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches, Dr. Ghazala Hayat (Ed.), InTech. https://www.intechopen.com/books/peripheral-neuropathy-advances-in-diagnostic-and-therapeutic-approaches/predictors-of-chemotherapy-induced-peripheral-neuropathy. Accessed 20 July 2018.

44. Wutthikonsammakit J, Chindavijak B, Chaikredkaew U, Lausoontornsiri W (2013) Study of Oxaliplatin-based Chemotherapy-Induced Neurotoxicity in Colorectal Cancer Thai Patients, Pharm Sci Asia. 2013; 40 (4), 8-16.

45. Tanaka A, Yoshino I, Makino S, Katsumata N, Takahashi K, Kuwano H, Maehara Y, Nishiyama M (2014) Questionnaire-based survey on chemotherapy-induced anaemia, Int J Clin Oncol. 19:411–420.

46. Chou T, Tobinai K, Uike N, Asakawa T, Saito I, Fukuda H, Mizoroki F, Ando K, Iida S, Ueda R, Tsukasaki K, Hotta T and the Lymphoma Study Group (LSG) of Japan Clinical Oncology Group (JCOG), Japan. (2011) Melphalan–Prednisolone and Vincristine–Doxorubicin–Dexamethasone Chemotherapy followed by Prednisolone/ Interferon Maintenance Therapy for Multiple Myeloma: Japan Clinical Oncology Group Study, JCOG0112, Jpn J Clin Oncol. 41(4)586–589.

47. Takenaka Y, Cho H, Yamamoto M, Nakahara S, Yamamoto Y, Inohara H (2013) Incidence and predictors of febrile neutropenia during chemotherapy in patients with head and neck cancer. Support Care Cancer 21(10):2861-8.

48. Shiota M, Yokomizo A, Takeuchi A, Kiyoshima K, Inokuchi J, Tatsugami K, Naito S (2014) Risk factors for febrile neutropenia in patients receiving docetaxel chemotherapy for castration-resistant prostate cancer. Support Care Cancer. 22:3219–3226.

49. Shiozawa T, Tadokoro J, Fujiki T, Fujino K, Kakihata K, Masatani S, Morita S, Gemma A, and Boku N (2013) Risk Factors for Severe Adverse Effects and Treatment-related Deaths in Japanese Patients Treated with Irinotecan-based Chemotherapy: A Postmarketing Survey. Jpn J Clin Oncol. 43(5) 483–491.

50. Sook H, Suk K, Lee Y, Won J, Yoon K, Choi J, In, Park H, Seok K, Jae L, Seo H, Won S, Yeul S, Kim H, Suk J, Kyong K, Park H (2016) Incidence and Predictors of Febrile Neutropenia among Early-Stage Breast Cancer Patients Receiving Anthracycline-Based Chemotherapy in Korea, Oncology. 91 (5):274-282.

51. Lin WT, Wen YW, Chien CR, Gau CS, Chiang SC, and Hsiao FY (2014) Suboptimal Duration of Granulocyte Colony–stimulating Factor Use and Chemotherapy-induced Neutropenia in Women Diagnosed with Breast Cancer. Clin Ther 36(9):1287-94.

52. Chan A, Chen C, Chiang J, Tan SH, Ng R (2012) Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy. Support Care Cancer. 20:1525–1532.

53. Wijayahadi N, Haron MR, Stanslas J, Yusuf Z (2007) Changes in cellular immunity during chemotherapy for primary breast cancer with anthracycline regimens. J Chemother 19(6):716-23.

54. Phua CE, Bustam AZ, Yusof MM, Saad M, Yip CH, Taib NA, Ng CH, Teh YC (2012). Risk of Treatment Related Death and Febrile Neutropenia with Taxane-Based Adjuvant Chemotherapy for Breast Cancer in a Middle-Income Country Outside a Clinical Trial Setting. Asian Pac J Cancer Prev. 13(9):4623-6.

55. Rajendranath R, Balasubramaniyum VK, Vijayakumar V, Ganesan P, Tenali GS (2014) Factors predicting outcome in high risk febrile neutropenia in patients receiving intensive chemotherapy for acute leukaemia: A prospective, observational study from South India. Indian J Cancer. Oct-Dec; 51(4):481-6.

56. Dattani N, Altham D, Coady K (2016) Neutropenia in Asian patients with solid tumours receiving chemotherapy: A retrospective case-control study, J Solid Tumours. Vol. 6, No. 2; 25-29.

57. MyVMC (2011) Chemotherapy-induced nausea and vomiting (CINV), Virtual Medical Centre https://www.myvmc.com/symptoms/chemotherapy-induced-nausea-and-vomiting-cinv/. Accessed 20 July 2018.

58. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol. 15:103–109.

59. Liau CT, Chu NM, Liu HE, Deuson R, Lien J, Chen JS (2005) Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians' and nurses' estimation vs. patients' reported outcomes. Support Care Cancer. 13: 277–286.

60. Kim HK, Hsieh R, Chan A, Yu S, Han B, Gao Y, Baños A, Ying X, Burke TA, Keefe DM (2015) Impact of CINV in earlier cycles on CINV and chemotherapy regimen

modification in subsequent cycles in Asia Pacific clinical practice. Support Care Cancer. Jan; 23(1):293-300.

61. Chan HK, Ismail S (2014) Side Effects of Chemotherapy among Cancer Patients in a Malaysian General Hospital: Experiences, Perceptions and Informational Needs from Clinical Pharmacists, Asian Pac J Cancer Prev, 15 (13), 5305-5309.

62. Perwitasari DA, Atthobari J, Mustofa M, Dwiprahasto I, Hakimi M, Gelderblom H, Putter H, Nortier JW, Guchelaar HJ, Kaptein AA (2012) Impact of Chemotherapy -Induced Nausea and Vomiting on Quality of Life in Indonesian Patients with Gynaecologic Cancer. Int J Gynecol Cancer 22(1):139-45.

63. Bourdeanu L, Frankel P, Yu W, Hendrix G, Pal S, Badr L, Somlo G, Luu T (2012) Chemotherapy-Induced Nausea and Vomiting in Asian Women with Breast Cancer Receiving Anthracycline-Based Adjuvant Chemotherapy. J Support Oncol. 10:149–154.

64. Pérez-Fidalgo JA, Roselló S, García-Garré E, Jordá E, Martín-Martorell P, Bermejo B, Chirivella I, Guzman C, Lluch A (2010) Incidence of chemotherapy-induced amenorrhea in hormone-sensitive breast cancer patients: the impact of addition of taxanes to anthracycline-based regimens. Breast Cancer Res Treat 120(1):245-51

65. Zhou W, Ding Q, Liang X, He Z, Zha X, Liu X, Wang S (2012) The Risk of Amenorrhea Is Related to Chemotherapy-Induced Leucopoenia in Breast Cancer Patients Receiving Epirubicin and Taxane Based Chemotherapy. PLoS One. 7(5):e37249

66. Liem GS, Mo FK, Pang E, Suen JJ, Tang NL, Lee KM, Yip CH, Tam WH, Ng R, Koh J, Yip CC, Kong GW, Yeo W (2015) Chemotherapy -Related Amenorrhea and Menopause in Young Chinese Breast Cancer Patients: Analysis on Incidence, Risk Factors and Serum Hormone Profiles. PLoS One 10(10): e0140842.

67. Tiong V, Rozita AM, Taib NA, Yip CH, Ng CH (2014) Incidence of chemotherapy-induced ovarian failure in premenopausal women undergoing chemotherapy for breast cancer. World J Surg 38(9):2288-96.

68. Choi EK, Kim IR, Chang O, Kang D, Nam SJ, Lee JE, Lee SK, Im YH, Park YH, Yang JH, Cho J (2014) Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. Psycho-Oncology. 23: 1103–1110.

69. Ra HS, Shin SJ, Kim JH, Lim H, Cho BC, Roh MR (2013) The impact of dermatological toxicities of anti-cancer therapy on the dermatological quality of life of cancer patients. J Eur Acad Dermatol Venereol 27(1): e53-9.

70. Yamada R, Sotozono C, Nakamura T, Nishida A Nakanishi S, Hirabatake M, Tsuji A, Kurimoto Y (2016) Predictive factors for ocular complications caused by anticancer drug S-1. Jpn J Ophthalmol 60(2):63-71.

71. Comets E, Ikeda K, Hoff P, Fumoleau P, Wanders J, Tanigawara Y (2003) Comparison of the pharmacokinetics of S-1, an oral anticancer agent, in Western and Japanese patients. J Pharmacokinet Pharmacodyn 30 (4):257-83.