Hepatocellular carcinoma in sub-Saharan Africa – the way forward

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Michael Kew's academic career spans five decades, representing the most proliferative and pioneering years of the expanded knowledge on all aspects of hepatocellular cancer (HCC). The preceding articles in this Festschrift bear testimony to his legacy, engagement, enthusiasm, dedication and ability to inspire others. His enormous contribution, mostly originating from research in sub-Saharan Africa (SSA), contributed immensely to the knowledge and evidence on which current understanding of the disease is based.

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The extent and magnitude of the advances made in the understanding and management of HCC becomes apparent when one browses an editorial published by Michael Kew in *Hepatology* in 1981.[1] At that stage, known aetiological factors for HCC included chronic hepatitis B virus (HBV) infection, cirrhosis, toxins (industrial chemicals and aflatoxin) and to a lesser extent α-antitrypsin deficiency, anabolic steroids and oral contraceptives. There was speculation of the possible role of as yet unidentified oncogenic viruses (non-A, non-B hepatitis viruses). Treatment options were limited and results were generally dismal. In a review published in 1982, Oon and Friedman[2] described surgery as 'infrequently attempted and rarely effective' and furthermore, any hope that surgery would be the ideal therapy as 'illusory'. Conventional radiotherapy was reported as unproven and results of chemotherapy trials were considered to be generally unsatisfactory. Median overall survival periods ranged from 3 - 6 months for patients undergoing conventional radiotherapy and survival rates following chemo-radiation at 1 and 2 years were 20% and 10%, respectively.

A review article published in 2018 presents a different perspective.[3] Since 1981, the non-A, non-B hepatitis viruses have been characterised and named as hepatitis C, D, E and G viruses. New aetiologies have emerged, of which the most important numerically, following the international epidemic of obesity and the metabolic syndrome, is non-alcoholic fatty liver disease (NAFLD). Modern epidemiological analyses have mapped international HCC disease trends more accurately with, notably, an estimated 80% of worldwide cases occurring in (SSA) and eastern Asia. Importantly, based on a better understanding of the aetiology and pathogenesis of HCC, prevention strategies have been developed. Primary prevention, including health education, vaccination and more effective antiviral therapies, has been introduced. The impact of primary prevention programmes on the incidence of HCC has been dramatic in populations where primary prevention programmes have been effectively applied.[4] Specific groups at risk for developing HCC have been defined and secondary prevention protocols together with screening and surveillance programmes have been devised, with the aim of diagnosing tumours at an earlier stage where, curative-intended intervention is still a feasible option. These prevention strategies, with slight variation, are included in and recommended by all regional guidelines.[5-9] The value of screening programmes is controversial, raising concerns such as false-positive testing which may result in unnecessary and potentially risk-associated procedures such as liver biopsy, and false-negative investigations which may result in a delay in the diagnosis of HCC, all potentially eroding cost-effectiveness.[10] Although the rationale for HCC surveillance is generally acknowledged, it needs to be optimised, especially in resource-challenged environments, with optimal patient selection and consideration given to risks v. benefits. This has important health economic implications. Furthermore, diagnostic algorithms have been refined, allowing non-invasive confirmation in the majority of patients, with invasive biopsy required in a minority.[11] Modern curative-intended treatment interventions include local ablation, surgical resection and transplantation, with trans-arterial embolisation and tyrosine-kinase inhibitors accepted as palliative modalities. All HCC guidelines include treatment algorithms that provide guidance for treatment decision-making and platforms for clinical trials.[12]

In populations where screening programmes are in place and where all diagnostic and treatment modalities are available, as many as 40% of patients are eligible for curative-intended interventions. In addition, where disease stage, underlying liver disease or the general condition of the patient or a combination of all these factors preclude curative interventions, up to 50% of patients will receive some form tumour-targeting treatment as part of palliative therapy, aimed at increasing overall survival. Five-year overall survival rates of around 70% for all three curative modalities have been reported where guidelines are followed. In addition, a number of studies have reported reasonable results when patients are treated beyond the criteria specified in the guidelines.[13-15] Although survival benefits with treatment with the tyrosine-kinase inhibitors are at best modest, increased survival of 16 - 20 months can be expected in patients treated with chemo- or radio-embolisation.[16,17]

In summary, although the management of HCC has presented many challenges, achievements over the last half-century have given a touch of optimism. Sadly, the advances in the management of HCC as presented have, with the exception of a few small and selected privileged populations, not benefitted patients with HCC in SSA.

HCC in sub-Saharan Africa

Differences in disease patterns between SSA black Africans and

inhabitants of the Western world have been reported in a number of papers published in the late 1970s and 1980s.[1,28-21] So great were the differences in the two population groups that one could have suggested two different diseases processes.[1] In SSA, chronic HBV infection and aflatoxin exposure were identified as the major aetiological factors, with an annual reported incidence as high as 103.8 per 100 000 population, compared with an annual incidence of 1 - 7 per 100 000 in non-African populations. The disease was characterised by a male predominance of 8:1, compared with 2.5:1 in non-African populations and a younger age of onset, mean age of 33.4 - 47.5 years as opposed to a mean of 60 - 80 years in non-African cohorts. The clinical presentation in SSA was more often associated with tumour-related symptoms and complicated disease due to tumour rupture and bleeding. Tumour growth was more rapid and patients presented with larger tumour burdens, resulting in resectability rates as low as 1%.[1]

The outcomes of patients with HCC in SSA are as poor as they were in Prof. Kew's pioneering years. The only change has been improved and more accurate documentation of the dismal presentation and prognosis. Chronic HBV infection remains the most compelling aetiological factor. Annual incidences for SSA populations continue to exceed the numbers in other regions, including other high-prevalence countries, such as China. Statistics for SSA, however, are flawed, unreliable and from many countries non-existent. Thus the true incidence of HCC is likely to be under-estimated.[22] The male predominance and younger age of disease onset prevails, and the disease stage at presentation is still more advanced, compared with non-SSA populations.[23]

Disturbingly, despite the fact that research produced from Africa has significantly contributed to global advances in the understanding and management of HCC, it has not translated into benefit for SSA patients.[24] With a few exceptions, the successes with primary prevention, surveillance and screening reported elsewhere could not be reproduced in SSA, even if risk groups are well defined.[25] The non-availability of diagnostic modalities makes diagnostic and management algorithms in existing clinical practice guidance of little relevance.[26] In the Global Surgery 2030 document published by The Lancet Commission in 2015, eastern, western and central SSA were identified as the regions in the world with the greatest unmet needs in surgical care.[27] In an almost perverse coincidence, it matches perfectly the regions in SSA with the highest incidence of HCC.[28] Surgical resection and local ablation are only available at a small number of larger centres, and liver transplantation is only performed at two centres in South Africa. In a recently published retrospective observational cohort study, which included data from 8 SSA countries, only 8 of 1 315 analysed patients (0.6%) underwent liver resection.[29] In the same study five patients (0.3%) underwent TACE and 12 patients (1%) received a tyrosine-kinase inhibitor.

A further concern is the effect that a lack of palliative resources has on the 99% of SSA patients who are primarily treated with palliative intent. Despite some recent advances, there is still minimal to no identified palliative care available in most African countries.[30] It is estimated that 88% of patients dying from cancer in SSA, and experiencing moderate to severe pain, are untreated.[32] This is the result of combinations of regulatory restrictions, a general lack of knowledge, lack of healthcare provider training on the use of opioids in palliative care and so-called 'opiophobia' due to misplaced fears of digestive side-effects and addiction.[32]

Lastly, in stark contrast to the hive of HCC research activity SSA once had, less than 1% of currently ongoing clinical HCC trials are conducted on the continent.[33] A number of factors account for this, including the challenges of conducting research in an area lacking support and infrastructure, and a tendency of industry to focus research on well-resourced populations, where the return on investments are greater compared with returns in the indigent populations on a forgotten continent.

The way forward

In an editorial 'Whither hepatocellular carcinoma in sub-Saharan Africa?' in the *African Journal of Cancer* in 2011, Mike Kew summarised the disturbing situation of HCC management in Africa, elucidating the complexity of the problem.[34] The same rhetorical question must have been posed many times during the past half a century and has a perpetual presence, either explicit or as a subliminal echo in papers on the topic originating from the continent. Numerous factors contribute to the dire situation and the generic inventory – poorly managed and funded healthcare systems, cost of treatment, suboptimal execution of vaccination programmes, shortage of healthcare professionals and equipment, and the absence of adaptable guidelines – are listed in most papers on HCC in SSA.[25,35] These conditions have made it difficult to effectively address the issue and have to some extent been used to legitimise failed initiatives. Some aspects of this multifaceted problem warrant closer scrutiny.

There are no guidelines specifically tailored to the situation in SSA. The spectrum of different available guidelines bears testimony to the diversity in regions, and although many of the guidelines are generic, there are differences in the management algorithms that are specifically made-to-measure to cater for special conditions in targeted populations.[36] The inhomogeneity in different SSA regions, between countries and even within countries, precludes a 'one size fits all' solution and will require management guidelines that are diverse and take into account the unique disease patterns, management options and available resources. This will be best achieved by incorporation of resource-sensitive algorithms catering for the diversity in SSA.[37] Guidelines should include modules for constant re-assessment. They should furthermore be dynamic and flexible, and responsive to changes in aetiology and epidemiology, as well as allow for adaption and realignment of treatment measures as influenced by the impact of preventive measures and strategies.

HCC fulfils the 10 fundamental requirements for a condition where screening is likely to improve outcome.[38] Although there is some discussion on the appropriateness of current screening methods, there is general consensus that the rationale for HCC screening is legitimate.[10,39] The high incidence of HCC in SSA, with less diverse aetiological factors and a higher prevalence in chronic HBV-associated tumours in non-cirrhotic livers, increases the likelihood of successful and health-economically sound screening, with careful selection of the most beneficial group of patients, which should yield a high advantage based on the incidence.

Interventional capabilities will have to be expanded in parallel to the developments in guidance on screening and surveillance in order to make the whole endeavour meaningful. Whereas success in primary prevention will reduce the need for secondary prevention, as well as curative and palliative treatment resources, secondary prevention with screening and surveillance will increase the need for curative-intended interventions, and probably will also increase the need for palliative interventions. The benefits of developing these capabilities will extend far beyond HCC, with the rising incidence of other conditions, such as colorectal cancer, and the subsequent need for treatment of liver metastatic disease that will need to be addressed.

In December 2017, the Gastroenterology and Hepatology Association of SSA (GHASSA) was launched in Cape Town during

the 8th Annual Liver Interest Group Meeting of the Gastroenterology Foundation of SSA. During a 2-day meeting on the eradication of viral hepatitis and screening for and treatment of HCC in SSA, the problem was discussed in detail. This meeting was attended by physicians and surgeons from 15 SSA countries representing west, east, central and southern Africa. An inventory of existing programmes in the region rendered a number of ongoing initiatives, including collaborative programmes, partnerships, fellowship programs and research cooperation, not only between institutions in SSA and abroad, but also between institutions on the continent.[18,40,41] It became evident that there are a number of tested successful templates that have made strides in advancing HCC care in some regions. Integration of these concepts into a comprehensive strategy can potentially have a synergistic effect. As part of the strategy, both failed and successful endeavours should be critically assessed. Efforts should be broad-based and should include all components of delivering modern healthcare, namely health policy makers, academic and research institutions, clinicians, health economics experts and the industry. Meticulous documentation should be integrated in endeavours to assess outcomes and facilitate outcome studies that will form the basis for future practice adjustments.

Advances in research techniques and technology will greatly facilitate this intergrated initiative. Comprehensive in-depth analyses of the current disease situation and inventories of infrastructure are greatly facilitated by the availability and accessibility of data in the information age. Using these data, modelling can be used to guide projections once the impact of measures are factored in and incorportating population dynamics in order to optimally prioritise and allocate resources. Telemedicine technology using teleguidance and telementoring on a small scale as well as in the context of large ventures, such as the Extension for Community Healthcare Outcomes (ECHO) project, will greatly facilitate this initiative.[42]

Conclusion

Insanity, as defined by some, is doing the same thing over and over again, but expecting different results. Whereas the issues that contribute to the unsatisfactory state of HCC management in SSA have not changed, new innovative approaches are needed to address the problem. During the meeting in Cape Town in 2017 it became apparent that there is a new generation of enthusiastic, dynamic and knowledgeable African clinicians who are able and eager to drive this initiative. Improving the fate of HCC patients in SSA will embody and honour the vision of early African pioneers and ensure their lasting legacy.

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