AYA Testis Cancer: the Unmet Challenge

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Abbreviations: AYA – adolescent and young adult; SMN – second malignant neoplasms; CVD – cardiovascular disease; GCT- germ cell tumours; OS – overall survival; SES- socio-economic status; CCS – cancer specific survival; YST – yolk sac tumour; MMGCT -mixed malignant GCT; NSGCT-non-seminomatous GCT; mRNA – messenger RNA; RPLND - retroperitoneal lymph node dissection; TCS -testicular cancer survivors; MRD- minimal residual disease; miRNA –microRNAs; BEP - cisplatin, etoposide and bleomycin; MaGIC- the Malignant Germ Cell International Consortium.

Abstract

Testis cancer is considered a rare-incidence cancer but comprises the third most common cancer diagnosed within the AYA years (15-39y). Most testis cancer patients can anticipate a survival outcome in excess of 95%. However, there are subgroups of AYA patients where outcomes are considerably worse including younger adolescents, patients with certain histological subtypes, or from certain ethnic backgrounds. For those cured with chemotherapy, the toxicity of treatment and burden of late-effects is significant. Newer germ cell tumour - specific biomarkers may identify

patients that do not require further treatment interventions or may detect early recurrence, potentially reducing the burden of treatment required for cure. International collaboration for this rare tumour is creating the forum for trial design, where these biomarker research questions are embedded. Going forward, AYA testis cancer patients could benefit from having a more personalised treatment plan, tailored to risk, that minimises the overall burden of late-effects.

Introduction

AYA cancer patients are a unique population; presenting with age-specific cancer diagnoses, differing tolerances to conventional therapies and often differing survival outcomes.⁽¹⁾

As cancer constitutes the most common cause of disease-related deaths in this age-group, health-care provision has become focused on working towards an understanding of how to provide better age-related outcomes of survival and experience of

care during and after treatment. ⁽²⁾

Whilst there has been much progress, particularly with regard to how to create an environment to accommodate the specific psychosocial needs for AYA patients, there is still much to learn about how to provide optimal survival outcomes.

Testicular cancer is an excellent example of this challenge. It is the most common cancer diagnosed in men under age 40 years (y). ⁽³⁾ Germ cell tumours (GCT) are considered to be a curable cancer, with overall survival (OS) for all patients approaching 96%. ⁽⁴⁾ However, adolescents diagnosed with a GCT are at risk of inferior outcomes when compared with either affected children or older adults. ⁽⁵⁾ More recent reports suggest that the broader range of AYA patients (between age 15-39y) do better than older men diagnosed with certain histological subtypes of testis cancer. ⁽⁶⁾ So how can we ensure we identify and provide effective therapies to accommodate these subgroups of patients who are most at risk?

The peak incidence of GCT occurs at 30y, with the natural incidence of testis cancer spread across the entire AYA range. ⁽⁴⁾ There is both geographical and ethnic variation in incidence within AYA, with white men in developed nations being disproportionately affected. ^(7, 8) However, this largest group of patients also tends to have the best outcomes. Analysis of the impact of ethnicity and socioeconomic status (SES) has shown that African American and Hispanic populations have poorer cancer specific survival (CSS), even when corrected for SES. ^(8, 9) Thus, within AYA testis can-

cer, we can identify another ‘at risk’ subgroup. What we understand less well is why these young men are more vulnerable to adverse outcomes. Here, we will discuss whether such outcomes can be accounted for by explanations other than poor access to health care for those not insured:⁽¹⁰⁾ specifically whether diagnostic delays or presence of more advanced disease at presentation; different histologic predominance or biologic behaviors can explain a survival gap.

The distribution and predominance of histologic subtypes of GCT varies with age. In children <11y the most common malignant histology is yolk sac tumor (YST). YST in children are generally exquisitely chemo-sensitive, and offer excellent outcomes after treatment, even in the face of advanced metastatic disease.⁽¹¹⁾ However, within the AYA years, mixed malignant GCT (MMGCT) becomes the most common histology.⁽⁴⁾ As age increases across the AYA range, there is relative increase in percentage of seminoma diagnoses represented, until ultimately seminoma overtakes MMGCT as the most common histological diagnosis (Figure 1). The 5 year CSS for either localized or metastatic MMGCT is less than for YST or seminoma in the same age-range.⁽⁴⁾ Pure choriocarcinoma, an aggressive non-seminomatous GCT (NSGCT) subtype which may present with a high burden of disease, remains rare. Hence, histologic subtype may in part contribute to the adolescent survival gap, but does not completely account for all of the discrepancy observed.⁽¹²⁾

Do AYA patients present later and have a higher burden of disease?

Localized disease is by far the most common presentation of testis cancer; approximately four-fold more common than a presentation with either regional or distant metastatic disease.⁽⁴⁾ (Figure 2) OS from localized disease is 95%. However, in patients aged between 10-15y, <50% patients present with localized disease. Of the remaining patients in this younger age-group, up to a third of patients are diagnosed with metastatic disease; a much higher rate than in any other age group.⁽⁴⁾ Veneroni et al found that adolescents had a longer symptom interval (SI) to diagnosis than children⁽¹³⁾. For adolescents with either locally or regionally advanced GCT, delays can worsen prognosis.⁽¹⁴⁾ However the relationship between SI and overall survival is complex, multifactorial and must also take into account the tumour's biological behavior.⁽¹⁵⁾

Can we identify the relationship between histologic subtypes within AYA and the burden of disease at presentation?

Seminoma presents with localized disease in up to 80% of patients, across all ages.⁽⁴⁾ In contrast, <50% of AYA diagnosed with a NSGCT have localized disease.⁽⁴⁾ The MMGCT subtype, the most common form of NSGCT in adolescents, presents with metastatic disease three-fold more commonly than patients with seminoma.⁽⁴⁾ Among AYAs, choriocarcinoma was the histologic type with the most advanced stage at diagnosis with up to 60% having regional or metastatic disease, but as it is rare, it has a minimal impact on overall survival outcomes.⁽⁴⁾

Hence, as both histology and younger AYA age at diagnosis correlate with a greater burden of disease, there is a consequent higher burden of therapy required for cure.

How does initial burden of disease, histology and patient age relate to outcome for AYA?

Overall an AYA patient with either localized disease or loco-regional disease can expect OS in excess of 95%. ⁽⁴⁾ However, an AYA patient with distant metastatic disease can anticipate a considerably lower chance of survival, between 70-80%. ⁽⁴⁾ For those who succumb to disease, within the AYA range, the age at which death is most likely to occur is between 20-24y. This anomaly has not changed for over 20 years. ⁽⁴⁾

Amini *et al* found that patients < 20y in the U.S., were managed more aggressively with surgery compared with the wider adult population, and received higher administration rates of adjuvant chemotherapy. ⁽¹⁶⁾ Conceivably, the higher surgical intervention rate and more aggressive surgery performed, is explained by the higher incidence of NSGCT relative to seminoma in this age-group and a higher burden of disease at presentation . However, AYA patients generally had less co-morbidity recorded during treatment and more often received care in high volume centers, both factors normally associated with better outcomes. ^(6, 17) In contrast, AYA patients diagnosed with seminoma have earlier stage disease at presentation, are treated with surveillance more frequently and have a slight OS advantage over older men. ⁽⁶⁾,

Additional factors to consider which may affect patient outcomes include the less well understood role of pharmacodynamics and pharmacokinetics. Eating disorders,

e.g. anorexia, bulimia, and obesity, all seen in the AYA age group, may have a prominent effect on drug distribution, sensitivity, efficacy, toxicity, and dosing.⁽¹⁸⁾ Hence, more intervention may translate into better outcomes, but can translate into a greater burden of potential late-effects for an individual.

Can our understanding of biologic behavior of GCT across different ages guide our interventional strategies to accommodate for survival discrepancies?

GCT in pre-pubertal children generally show fundamental molecular differences to those in adult patients, despite sharing a similar histology, which suggests that basing clinical management purely on chronological age or histology alone may not provide optimal treatment strategies for AYA patients.⁽¹⁹⁾

Regarding genomic changes, gain of the short arm of chromosome 12 (12p) is an almost universal finding in adult testicular GCT patients.^(20, 21) Gain of 12p was identified in 5/18 (27%) male pediatric GCTs in one study⁽²²⁾ and 44% in another.⁽²³⁾ The incidence of 12p gain increased with patient age (29% <5y; 53% 5-16y)⁽²³⁾. Thus, genomic copy number imbalances distinguish GCT subgroups primarily by age, rather than by tumor site or histology⁽¹⁹⁾. However, for the AYA population, the prognostic significance of 12p gain and other genomic imbalances seen in GCTs is yet to be determined.

At a transcriptomic level, pediatric GCT have a distinct protein-coding (messenger RNA- mRNA) gene expression program compared with adult GCTs, irrespective of tumor site⁽²⁴⁾. Furthermore, pediatric and adult tumors with comparable histology (seminoma, YST) were also segregated by global mRNA expression profiles, lending weight to the suggestion that the clinical management of these entities should be different⁽²⁴⁾. Interestingly, a very small number of pediatric GCTs had 'adult' profiles and *vice versa*⁽²⁴⁾; the significance of such findings needs to be elucidated in further studies, and interrogation of biospecimens from an AYA cohort will likely facilitate this. An mRNA signature predictive of outcome has been reported in metastatic NSGCT patients (median age 29y; range 15-60y), which added independent prognostic accuracy to existing risk classification systems⁽²⁵⁾. However, translation of this multi-gene signature into clinical practice will be challenging and, it remains unclear whether this predictive model would be applicable for pediatric or younger AYA (13-24y) populations.^(19, 26)

Do AYA have suboptimal treatment strategies/cure vs. Quality of life for AYA – have we got the balance right?

Adult testis cancer is viewed as the success story for a curable cancer. However, this cure is not without significant cost in the longer term. The burden of late effects is both wide in range and significant in impact for all men requiring adjuvant treatment. They include an increased risk of second malignant neoplasm (SMN); early onset cardiovascular disease (CVD); hypogonadism; infertility; peripheral neurotoxi-

city; tinnitus and hearing loss; renal toxicity; pulmonary toxicity; fatigue; and anxiety and depression.

After mortality, fertility is the second most common concern for patients with cancer.

⁽²⁷⁾ This is of particular concern for younger AYA patients diagnosed and treated for cancer at a time in life when many have not made choices around starting a family, let alone completion. The link between reduced fertility and cancer starts at diagnosis and up to to 50% of post-orchietomy patients have been shown to have decreased sperm counts, with some patients also having low sperm motility and abnormal sperm cells. ⁽²⁸⁾

Further components of testicular cancer therapy, namely retroperitoneal lymph node dissection (RPLND), radiotherapy and chemotherapy, all come with differing fertility risks. For patients requiring chemotherapy for cure, the cumulative dose of cisplatin-based treatment is directly associated with the risk of infertility and achievement of paternity. ^(29, 30, 31,) Conversely, the use of carboplatin-based regimens, directly compared with cisplatin, has been shown to be associated with fourfold greater recovery to normal sperm counts. ⁽³²⁾ The majority of AYA patients will be diagnosed with a NSGCT and will receive 'adult' BEP.

Up to a third of patients with NSGCT metastatic disease may require consideration of a RPLND following chemotherapy. RPLND is associated with significant potential morbidity, both in the peri-operative period and in the long-term. In the post-chemotherapy setting, the gold standard for surgery remains a bilateral template dis-

section via an open approach. ⁽³³⁾ If the retroperitoneal postganglionic sympathetic nerves are damaged intra-operatively, this surgical procedure carries the risk of inducing retrograde ejaculation in up to 9% of patients. ⁽³⁴⁾

Radiotherapy (RT) has played an important adjuvant role in advanced stage seminoma therapy for many years, and for most patients, there is recovery of normal spermatogenesis within 24 months of end of treatment ^(30,35) . In long-term follow-up, when compared with a surgery-only cohort, there appears to be no significant impact on spermatogenesis. ^(30, 35) Thus overall, RT is less likely to be implicated in any loss of fertility for AYA patients, as fewer AYA patients will require RT.

Hypogonadism contributes to the risk of infertility. Causes of hypogonadism include orchiectomy itself, chemotherapy, radiotherapy and any underlying testicular dysgenesis syndrome. The additional side effects of hypogonadism include reduced sexual functioning, depression, fatigue, loss of muscle mass and osteoporosis. Furthermore, the known association between the metabolic syndrome and CVD as a direct result of hypogonadism adds substantially to the burden of late-effects. ⁽³⁶⁾

The risk of early onset CVD is of particular concern. The relative risk of CVD in patients treated with chemotherapy is 1.4-7.1 fold higher compared with the general population or those patients undergoing surgery alone. ^(36, 37, 38) Hypogonadism, together with chemotherapy-induced vascular injury and chemotherapy-related disturbance of metabolic homeostasis, combine ⁽³⁹⁾ to increase CVD mortality risk. In a

population based study, Fung *et al* described patients appearing to be at most risk within the first year off treatment, with a calculated 5.3-fold risk of mortality.⁽⁴⁰⁾

SMN constitutes a significant cause of morbidity and mortality. Post-chemotherapy, there is an increased risk of both solid and leukemic SMNs. Kollmansberger *et al* reported that the 5 year cumulative incidence of secondary leukemia after a cumulative etoposide dose of $<2000\text{mg/m}^2$ and $>2000\text{mg/m}^2$ was approximately 0.5% and 2.0%, respectively.⁽⁴¹⁾ Similarly, when Fung *et al* reviewed the risk of solid tumor SMN, a 1.4-fold increase risk for those who had received chemotherapy compared with those who underwent surgery alone was identified.⁽⁴²⁾ Therefore, not only the choice of chemotherapy drugs, but also the dosing of these drugs, appears to be important.

Long-term renal dysfunction has been directly associated with cumulative dosing of cisplatin.⁽⁴³⁾ Up to 40% of testicular cancer survivors (TCS) experience symptoms of peripheral neuropathy during and/or after chemotherapy.^(44, 45) Non-fatal pulmonary toxicity has been reported between 7-21% of TCS.^(46, 47) Risk factors for restrictive lung disease included cisplatin dose and increasing age, after adjusting for bleomycin, etoposide and vinblastine exposure.⁽⁴⁸⁾ For TCS treated with chemotherapy, there was a higher mortality rate from all respiratory diseases when compared with the general population.⁽⁴⁹⁾

Ototoxicity secondary to cisplatin may also have a significant impact on quality-of-life.^(50, 51) Bokemeyer *et al* reported symptomatic ototoxicity in 20% of testicular cancer survivors.⁽⁵²⁾ Tinnitus was the most reported symptom in 59% patients, but

23% reported both tinnitus and hearing loss together. Dose was important, with 50% of patients receiving $>400\text{mg/m}^2$ cisplatin experiencing persistent ototoxicity. ⁽⁵²⁾

One of the late effects TCS find most distressing is fatigue; it is often the most frequently reported concern in long-term follow-up. ⁽⁵³⁾ The prevalence of depression in up to 20% of TCS has been reported widely ^(54, 55, 56, and 57) with anxiety significantly associated with younger age at diagnosis. ⁽⁵⁵⁾ AYA patients are already known to be more likely to suffer psychological problems after a cancer diagnosis and greater difficulty in retaining employment or maintaining education. ^(58, 58, 60)

Many AYAs with cancer report that their cancer makes them feel 'abnormal'. ⁽⁶¹⁾ TCS describe difficulty both with romantic partnerships and support. ⁽⁶²⁾ Anxieties around body image and masculinity arise when changes in appearance (e.g. scarring, loss of hair/body parts etc.) result in diminishment of sexual attractiveness. ^(61, 62) Bellizzi *et al*, in the AYA HOPE study, showed that over 50% of TCS reported they felt like 'damaged goods' due to surgical scars and loss of a testicle and had concerns about their ability to have children. ^(60, 61, 62)

Although a cancer diagnosis may be disruptive to normal social maturation for an AYA patient ^(63, 64), TCS considered that those who had not experienced testicular cancer could not understand how the experience had shaped their life views on maturing and growing up. They considered the experience provided them with a unique, but different, outlook on life, marriage and parenthood compared with their peers. ⁽⁶¹⁾

Hence for a common cancer in this AYA age range, for patients with many life years ahead, the burden of late-effects can be profound.

What can we do to reduce burden of therapy? Personalizing the treatment plan.

A better understanding of the absolute need for surgery, radiotherapy and intensity of chemotherapy regimens could mitigate against some late-effects. Minimal residual disease (MRD) testing by highly sensitive PCR techniques has been transformative for patients with ALL; allowing a more elegant risk stratification to inform the burden of therapy.⁽⁶⁵⁾

The emergence of microRNAs (miRNA) as a biomarker of disease could potentially help risk-stratify the burden of therapy required for cure in a way analogous to MRD for ALL patients i.e. allowing understanding of ‘molecular remission’ and no requirement for any further treatment intervention. MiRNAs are short, non-coding RNAs that modulate protein-coding gene expression, through interactions with specific binding sites in the 3’ untranslated regions of messenger RNAs.⁽⁶⁶⁾ MiRNAs are dysregulated in cancer, acting either as oncogenes or tumor suppressor genes.⁽⁶⁷⁾

In GCTs, the most striking finding was universal miR-371~373 and miR-302/367 cluster over-expression in all malignant tumors, regardless of patient age (pediatric/AYA/adult), histologic subtype (YST/ seminoma) or anatomic site (gonadal/extragenadal).⁽⁶⁶⁾ Expression levels of just the eight main miRNAs from these two clusters accurately separated >100 malignant GCTs from non-malignant samples, suggesting that these miRNAs could offer high sensitivity and specificity as malignant GCT biomarkers⁽⁶⁶⁾.

Serum miRNAs have also been shown to be useful longitudinally for early sensitive detection of malignant recurrence in stage I disease and disease-monitoring following initiation of chemotherapy.⁽⁶⁸⁾ Serum miRNA testing and validation in prospective clinical trials (e.g. the Children's Oncology Group's trial AGCT1531) is now under way, heralding an opportunity for non-invasive monitoring and reduced use of serial CT scans with consequent radiation exposure during treatment and follow-up.⁽⁶⁹⁾ The potential methods of decreasing the morbidity of surgery in the future are likely to involve a decrease in the extent of surgical dissection, and the increased utilization of minimally invasive approaches, particularly robot-assisted RPLND. These methods are of particular significance in the AYA population. European and North American studies in high volume centers have shown that the use of modified unilateral templates for selected cases did not result in any recurrences within the field of a bilateral template dissection and did not compromise oncological outcomes, exemplifying that when RPLND is a fundamentally important for cure, referral to high volume centres with experienced uro-oncology surgeons is paramount.^(70, 71) Robotic RPLND in the post-chemotherapy setting is increasingly utilized. Small series have shown significant decreases in peri-operative morbidity, rates of retrograde ejaculation and hospital length of stay without compromise of oncological outcomes although long-term follow-up is not yet present.^(72, 73, 74)

For those AYA patients where chemotherapy remains essential for cure, we have a responsibility to develop less toxic but equally effective treatment regimens. Adult BEP chemotherapy (cisplatin, etoposide and bleomycin) remains the gold standard

treatment.⁽⁷⁵⁾ Carboplatin is a platinum agent that has not been demonstrated to have the same long-term toxicity profile as cisplatin. Historically, carboplatin regimens have been tested against cisplatin in the hope that carboplatin may provide equally effective survival outcomes but with less morbidity.^(76, 77, 78) These trials had concluded it was less effective than cisplatin. Recent reviews comparing these and other cisplatin and carboplatin outcomes, suggests we should re-consider its use across all ages, as inadequate dosing and frequency of delivery could account for the discrepancy in outcomes documented in the era before the use of stem-cell factor support.^(79, 80) Pharmacogenomics studies may further help finesse decision making.

How do we achieve this?

As a result of the above, the international GCT community needs to continue to advocate for all GCT patients, but in particular for AYA patients with testicular cancer where arguably much more remains unknown and unresolved. MaGIC (the Malignant Germ Cell International Consortium; <https://www.magicconsortium.com/>) is an international collaboration comprising clinicians and scientists from pediatric, medical, gynecological, clinical oncology and allied disciplines. International platforms such as MaGIC can begin to address geographic and ethnic variation in outcomes and ensure biology is embedded in new trial development. This strategy should allow us to locate these vulnerable subgroups of patients, reduce the burden of therapy and engage the groups of patients that are most at risk of late-effects in tailored re-

search programs. More locally, discussion of teenage GCT patients should always take place in a disease-specific multidisciplinary meeting with combined medical and paediatric oncology representation. This will facilitate sharing of expertise, promote enrolment into international trials open to AYA patients and adherence to national guidance to support safe delivery of care and minimize treatment related mortality.

Conclusion

The incidence of testicular cancer is increasing across all ages within the AYA spectrum (13-39y). Compared with older adult patients, AYA patients present with a higher burden of disease and with more NSGCT histologies which require more intensive treatment for cure; this inevitably translates into an increased burden of late effects. By contrast, for men aged >40y, the prevalence remains stable. Thus, for those patients with the most life years left to live, the numbers of patients requiring the most morbid treatment are increasing.

The identified miRNA signature, applicable across all patient ages, offers the potential for a universal test for diagnosis and disease-monitoring. Although the genomic and protein-coding gene molecular differences observed between pediatric and adult GCTs⁽¹⁹⁾ may well be triggered by puberty, most, but not all, AYA GCT are likely to be 'adult' tumors biologically, the lack of focus on this cohort to date makes this largely an assumption. Consequently, clinical management based simply on chronological patient

age may well be suboptimal. Future research focused on AYAs, particularly the younger AYA group (13-24y), may alleviate these challenges and facilitate more personalized clinical management including removal of disparities in access to health care as an issue. Moreover, such work may also allow more accurate prognostic risk groups to be defined and assist the development of novel therapies that have increased efficacy in poor-prognosis tumors and/or cause less long-term toxicity in good-prognosis patients. All this will be best achieved within a collaborative, international forum.

Conflict of Interest Statement:

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819 FIGURE 1 Histology Distribution of Testis Cancer, 2000-2011, SEER18, by Age

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FIGURE 2 Distribution of Stage of Testis Cancer, SEER 18, 2000-2011, by Age

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