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REVIEW

Major Advances in the Treatment of Cancer

What does a Non-Oncologist need to know?

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التطورات الرئيسية في علاج السرطان

ما يحتاج معرفته غير المتخصص في علم الأورام

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شهدت السنوات القليلة الماضية تطورات كبيرة في علاج مختلف أنواع السرطان. ونظرا إلى عدم إمكانية مواكبة آخر التطورات في مجال الأورام إلا من قبل المتخصصين في ذلك العلم . لخصنا في هذا التقرير أهم التطورات الحاصلة في علاج مختلف أنواع السرطان على مدى السنوات الأربع الماضية. في بعض المجالات حصل تحولا في وضع معايير جديدة للرعاية. على سبيل المثال، استخدام العلاج المستهدف (trastuzumab) كعلاج مساعد لسرطان الثدي، واستخدام الأجسام المضادة أحادية النسيلة (rituximab) مع أو بدون العلاج الكيميائي في معالجة ومداومة علاج اللمفوما المهاودة . واستخدام أنزيم مانع التيروزين كيناز (imatinib) كمساعد في تحديد الأورام المعدية المعوية السَدوِيةّ المستأصلة. وفي المجالات الأخرى ظهر أنواع أخرى من العلاج، مثل استعمال العلاجات المستهدفة في سرطان الكبد (torafenib)، سرطان خلايا الكلية . و (sunitinib, sorafenib, temsirolimus, bevacizumab) . وفي بعض أنواع السرطان كان لإضافة العلاجات المستهدفة دور في تحسين معدل البقاء، مثال ذلك سرطان القولون (bevacizumab, cetuximb, panitumumab) . سرطان الرأس والرقبة (cetuximab) . سرطانة البنكرياس الغدية (erlotinib). وفي مجموعة أخرى ظهرت علاجات مستهدفة أخرى عندما لوحظ أن هناك مقاومة للعلاجات المستهدفة الموجودة . مثال ذلك سرطان الثدي (lapatinib) , سرطان الدم النخاعي المزمن (dasatinib). وأخيرا وجد أن إضافة عوامل كيميائية علاجية حسنت البقاء في بعض أنواع السرطان . مثال ذلك (oxaliplatin) كعلاج مساعد في سرطان القولون . (temozolamide) في وَرَمٌ أَرومِيٌّ دِبْقِيٌّ مُتَعَدِدُ الأَشْكال وعلاج كيماوي مساعد في سرطان الرئة الذي لا يصيب الخلايا الصغيرة. هذه المعلومات الملخصة قد تفيد الأطباء الذين لا وقت لديهم والذين في الوقت نفسه يريدون معرفة الجديد في مجال علم الأورام.

مفتاح الكلمات: علم الأورام، تراستوزوماب، ريتوكسيماب ، ايمايتيناب، سورافينيب، سونيتينيب، بيفاسيزوماب.

ABSTRACT The last few years have seen major advances in the management of cancers. Since it is not possible for the non-oncologist to keep abreast with the latest developments in the field of oncology, this review summarises the most significant advances in the area of treatment of various cancers over the past four years. In some areas, a paradigm shift has occurred setting new standards of care, for example, the use of targeted therapy (trastuzumab) in adjuvant treatment of breast cancer; the use of monoclonal antibodies (rituximab), with or without chemotherapy, in the treatment and maintenance of indolent lymphoma; the use of the tyrosine kinase inhibitor, imatinib, in the adjuvant setting in resected gastrointestinal stromal tumours. In other areas, new treatments have emerged, such as, the use of targeted therapies in hepatocellular carcinoma (sorafenib) and renal cell carcinoma (sunitinib, sorafenib, temsirolimus, bevacizumab). In some other cancers, the addition of targeted therapies has improved survival rates, for example, in colon cancer (bevacizumab, cetuximb, panitumumab), head and neck cancers (cetuximab), and pancreatic adenocarcinoma (erlotinib). In yet another group, new targeted therapies have emerged where resistance was previously observed with the existing targeted therapies, for example, breast cancer (lapatinib), chronic myeloid leukemia (dasatinib). Finally, the addition of chemotherapeutic agents has improved survival in some forms of cancer, for example, oxaliplatin in adjuvant treatment of colon cancer, temozolamide in glioblastoma multiforme, and adjuvant chemotherapy in non-small cell lung cancer. The information summarized here may provide useful for the busy physician needing an update in the field of oncology.

Keywords: Medical Oncology; Trastuzumab; Rituximab; Imatinib; Sorafenib; Sunitinib; Bevacizumab.

The last few years have seen major advances in the management of cancers, which have changed the way these cancers are now managed. Some of the advances can easily be regarded as having changed the paradigm of cancer management, while others represent continued in-

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cremental gains. The management of cancers includes prevention, surveillance and early detection, treatment of early and advanced disease, and the issues related to long-term survival after the cure. For the purposes of this review, only advances related to treatment of the disease, both in adjuvant and palliative settings are described. Besides obtaining information from a review of the literature over the past four years, information was obtained from the series 'Clinical Cancer Advances' published in the Journal of Clinical Oncology for the past three years.[1-3] The cancer sites/organs are arranged in alphabetical order and the setting of treatment (adjuvant or palliative) are described where appropriate, as follows:

1. Breast cancer
2. Chronic myeloid leukemia (CML)
3. Colon cancer
4. Gastric cancer
5. Gastrointestinal stromal tumour (GIST)
6. Glioblastoma multiforme (GBM)
7. Head and neck cancer
8. Hepatocellular carcinoma (HCC)
9. Lung cancer
10. Multiple myeloma
11. Non-Hodgkin's lymphoma (NHL)
12. Ovarian cancer
13. Pancreatic cancer
14. Prostate cancer
15. Renal cell carcinoma (RCC)

BREAST CANCER

ADJUVANT TREATMENT

Adjuvant Trastuzumab improves survival when added to standard adjuvant chemotherapy

Since the publication of the meta-analysis establishing the role of adjuvant chemotherapy and hormonetherapy in early stage breast cancer, several important strides have been made. The addition of either anthracyclines (doxorubicin or epirubicin), and/or taxanes (paclitaxel or docetaxel) to cyclophosphamide with or without 5-flurouracil has been shown to improve disease free survival (DFS) and the overall survival (OS). The improvement in survival rates were of the order of 4-7% (absolute difference) at the end of 5 years.[4] More recently, the addition of trastuzumab to the chemotherapy has been shown to improve further the survival in patients with breast cancer expressing the HER-2/neu oncogene (also called c-erbB2). Around 25-30% women with breast cancer have the oncogene, causing expression of the protein on the cell surface, which is detected by either immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH). The protein is associated with an increased risk of cancer recurrence and a decreased sensitivity to some forms of chemotherapy.

Trastuzumab is a monoclonal antibody that blocks the protein HER-2/neu and had been in clinical use since at least 1998 for metastatic breast cancer, where together with palliative chemotherapy, the survival was shown to be prolonged in women treated with trastuzumab. Four randomised trials involving more than 13,000 women have been reported within the past 3 years, all leading to the same conclusion.[5-8] The analysis showed for the first time that adding trastuzumab to standard chemotherapy for early-stage breast cancer that expresses HER-2 reduced the risk of recurrence in women by almost half after three years compared with chemotherapy alone. The four trials varied in design to some extent, and the details are shown in Table 1.[5-8] The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial compared 4 cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel followed by observation or one calendar year of trastuzumab therapy. The Intergroup trial compared, in a three arm study, 4 cycles of doxorubicin and cylophosphamide followed by weekly paclitaxel for 12 weeks with either observation, concomitant trastuzumab with paclitaxel or sequential trastuzumab for one year. The Breast Cancer International Research Group (BCIRG), also in a three arm study, compared 4 cycles of doxorubicin and cylophosphamide followed by 4 cycles of docetaxel with either observation or trastuzumab for a year. The third arm consisted of 6 cycles of docetaxel and carboplatin followed by one year of trastuzumab. The fourth and the largest trial, the European Herceptin Adjuvant Trial (HERA), in addition to randomising patients between the observation and the trastuzumab arm after completion of the chemotherapy according to the institutional guidelines, also studied the relationship between duration of trastuzumab use (one year versus two years) and breast cancer recurrence in more than 5,000 women in 39 countries. Taken together, the four trials demonstrated that addition of adjuvant trastuzumab for one calendar year improves the DFS from 67% to 85% at 4 years. This degree of improvement

Table 1: ***Different treatment strategies employing trastuzumab in an adjuvant setting for breast cancer***

Trial	No of patients	Treatment Scheme
NSABP-31	1960	AC x 4 > Pac 3 weekly x 12 wks AC x 4 > Pac 3 weekly x 12 wks + Tras weekly x 52 wks
Intergroup N-9831	3046	AC x 4 > Pac weekly x 12 wks AC x 4 > Pac weekly x 12 wks + Tras weekly x 52 wks AC x 4 > Pac weekly x 12 wks > Tras weekly x 52 wks
BCIRG 006	3222	AC x 4 > Doc 3 weekly x 4 AC x 4 > Doc 3 weekly x 4 + Tras weekly > 3 wkly x 52 wks carboplatin + Doc 3 weekly x 6 + Tras 3 weekly x 52 wks
HERA	5090	Any CT±RT > Observation Any CT±RT > Tras 3 weekly for 12 months Any CT±RT > Tras 3 weekly for 24 months

NSABP = National Surgical Adjuvant Breast and Bowel Project; BCIRG = Breast Cancer International Research Group; HERA = Health, Empowerment, Research, and Awareness Foundation; AC = Doxorubicin + Cyclophosphamide; Pac = Paclitaxel; Doc = Docetaxel; Tras = Trastuzumab; CT = Chemotherapy; RT = Radiotherapy;

represents the most significant gain in survival in the history of adjuvant treatment of breast cancer.

However, the addition of trastuzumab was not free of side effects. All trials showed an increased risk of congestive heart failure associated with the drug.[8] The incidence of severe congestive heart failure or death from heart problems ranged from 2.9% and 4.1% in the women taking trastuzumab, versus up to 0.8% in the observation group group. In an attempt to reduce the cardiotoxicity, without compromising the survival gain, yet another trial called the FinHer trial, studied the possibility of using attenuated trastuzumab therapy for 9 weeks compared to the observation group.[9] The trial was small including only 232 women. Women in the trastuzumab group were significantly less likely to experience a recurrence with fewer cardiac side effects. With a longer follow-up, this trial might suggest that patients would be able to safely take a shorter course of the therapy, limiting the cost of the drug and the risk of serious side effects, without reducing efficacy.

However, currently, the individual and the pooled results of the four large clinical trials, represent a very significant advance in breast cancer treatment, and have already changed the standard of care for the women who express HER-2 protein.

Aromatase inhibitors improve the overall survival compared to tamoxifen in an adjuvant setting

Over the past 30 years, tamoxifen has been the standard of care for the adjuvant hormone treatment in hormone receptor positive early breast cancer.[4] In the last few years alone, three third-generation aromatase inhibitors (letrozole, anastrazole, and exemestane) have been shown to improve the DFS and the OS in the adjuvant setting. Previously these agents had been shown to be effective in metastatic breast cancer. More recently, the three agents have been investigated as adjuvant therapy of early breast cancer employing various treatment strategies: replacement of tamoxifen as adjuvant therapy for 5 years, sequencing of tamoxifen before or after an aromatase inhibitor during the first 5 years, or following 5 years of tamoxifen. In the first adjuvant trial (arimidex, tamoxifen alone or in combination [ATAC]), anastrozole was significantly superior to tamoxifen in reducing risk of disease recurrence.[10] The Breast International Group (BIG) trial BIG 1-98 demonstrated the significant superiority of letrozole over tamoxifen in improving disease-free survival.[11] A large trial (International Collaborative Cancer Group [ICCG] trial 96) investigated the sequencing of 2 to 3 years of exemestane after 2 to 3 years of tamoxifen and found that switching to exemestane was significantly superior in disease-free survival compared with continuing on tamoxifen.[12] Trial MA17 evaluated extended adjuvant therapy with letrozole versus a placebo following 5 years of tamoxifen. DFS was significantly improved with letrozole versus a placebo, irrespective of whether patients had lymph node-positive or node-negative tumours[13]. All three aromatase inhibitors are generally well tolerated. However, the long-term side effects remain to be studied. Results of these trials indicate that aromatase inhibitors provide important benefits relative to tamoxifen in each of these adjuvant treatment settings.

treatment of metastatic disease

Patients with HER-2/neu positive disease, who fail first line treatment with anthracycline, taxane and trastuzumab are usually treated with the prodrug of 5-fluorouracil, capecitabine. Recently two trials have been reported, in which a combination of either a tyrosine kinase inhibitor, or a chemotherapeutic agent of a novel class, epothilone, were found to be superior than capecitabine alone in terms of DFS. Lapatinib, a tyrosine kinase inhibitor of HER2/neu and epidermal growth factor receptor (EGFR),was used in combination with capecitabine in a Phase III international multicentre trial in patients expressing HER-2/neu protein.[14] Time to progression was almost twice as long in the lapatinib/capecitabine group: (36.9 weeks) compared with the capecitabine only group (19.7 weeks). The combination was well tolerated. In another Phase III trial, ixabepilone and capecitabine prolonged progression-free survival (PFS) (5.8 months) relative to capecitabine (4.2 months).[15] For the first time the PFS has been shown to be prolonged in this difficult-to-treat group of patients.

CHRONIC MYELOID LEUKEMIA

Since the approval of imatinib by the US Food and Drug Administration (FDA), the treatment of chronic myeloid leukaemia (CML) has been revolutionised so that very few patients now receive the toxic treatment of allogeneic bone marrow transplant. Imatinib is an inhibitor of the tyrosine kinase produced by a mutation in the BCR-ABL gene. However, some patients develop additional mutations in this gene, causing their cancers to become resistant to the drug. Dasatinib targets these secondary mutations. In a Phase I clinical trial to determine the optimal dose of dasatinib for those who could not tolerate or had become resistant to imatinib, 92.5% of the patients had no evidence of disease after receiving dasatinib.[16] Additionally, 70% of patients in the accelerated phase experienced a significant decrease in the number of blast cells after receiving dasatinib. The duration of benefit was dependent on the phase of the disease when the patient was treated. Dasatinib represents a significant improvement in the overall treatment of CML in general, and imatinib resistant cases in particular.

COLON CANCER

adjuvant treatment

Over the years, modulated 5-FU has remained the standard of care for fully resected Stage II and III colon cancer in the adjuvant setting. Several different regimens incorporating leucovorin with 5-FU given for 6 months, had been shown to reduce the recurrence rates by 40% in Stage III colon cancer, and a lesser degree in Stage II disease. More recently, one large study (the MOSAIC trial) found that adding oxaliplatin to standard chemotherapy after surgery for early-stage colorectal cancer reduced the risk of recurrence by 24%.[17] A separate study from the National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that adding oxaliplatin to standard chemotherapy reduced the risk of recurrence by 21% in early-stage colorectal cancer patients.[18] Coupled with similar data from other smaller studies, these findings have changed the treatment approach for patients with early-stage colorectal cancer who need chemotherapy after surgery.

treatment of metastatic disease

Three signal transduction inhibitors, bevacizumab, cetuximab, and pannitumab have been approved in the past three years for treatment of metastatic colorectal cancers in the first and the second line. Bevacizumab is a recombinant, humanised monoclonal antibody against vascular endothelial growth factor (VEGF) that is used to inhibit VEGF function in vascular endothelial cells and thereby inhibit tumour angiogenesis. The addition of bevacizumab to 5-FU, with or without irinotecan or oxaliplatin, in both the first- and second-line treatment of metastatic colorectal cancer, has been shown to significantly increase PFS in several randomised trials. The overall survival advantage attributable to bevacizumab is 4.7 months with first-line therapy and 2.1 months with second-line therapy.[19] Bevacizumab has acceptable tolerability, with the majority of adverse events being generally mild and clinically manageable; however, cost effectiveness remains a concern in this setting.

Another monoclonal antibody cetuximab, an inhibitor of the epidermal growth factor receptor (EGFR) has been shown, together with chemotherapy, to improve survival in metastatic colon cancer. A Phase III clinical trial involving patients with advanced colorectal cancer showed that the addition of cetuximab to a standard first-line chemotherapy combination called FOLFIRI (folinic acid, 5-FU, and irinotecan) reduced

the risk of progression by 15%.[20] Significantly more patients were able to undergo surgeryfor the complete removal of their tumours. In addition, more than twice as many patients with liver metastases were able to have their tumours completely removed in the cetuximab plus FOLFIRI group. The study was the first to evaluate this combination, providing a new treatment option and enabling more patients to have their tumours surgically removed.

GASTRIC CANCER

NEO-ADJUVANT AND ADJUVANT TREATMENT

Stomach cancer is conventionally regarded as a difficult tumour to treat and most of the patients diagnosed with it die of the cancer despite adequate surgery. Over the past 7 years, two significant advances have occurred, which have set new standards in the management of completely resected gastric cancer. A large U.S. Intergroup study (INT-0116) demonstrated that combined chemoradiation following complete gastric resection improves median time to relapse (30 versus 19 months, p <.0001) and overall survival (35 months versus 28 months, p =.01).[21] Subsequently, the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial, conducted in the UK, provided another significant advance. Neo-adjuvant chemotherapy, employing three cycles of a combination of epirubicin, cisplatin and 5-FU (ECF), was not only able to downsize several tumours, rendering them resectable , but was also associated with improvement in OS.[22] Three further cycles of the same regimen were administered after the resection in an adjuvant setting. The updated results of the MAGIC Trial showed that 36% of patients who received chemotherapy were still alive five years after diagnosis, compared with 23% of those who received surgery alone. Taken together, the results of the two trials have changed the standard of care of gastric cancer.

GASTROINTESTINAL STROMAL TUMOUR

Gastrointestinal stromal tumours (GIST) are characterised by the presence of c-kit receptor, which in turn can be blocked by imatinib. Imatinib has been in clinical use for the treatment of metastatic GIST for several years, and has response rates of up to 70%. Imatinib has also been used to downsize the large tumours, and make them amenable to surgery. More, recently, imatinib has been found to have improved the recurrence free survival (RFS) in patient with resected GIST when used in the adjuvant setting. A National Cancer Institute sponsored study randomised patients to receive either 1 year of imatinib, or a placebo after completely resecting the GIST.[23] At the end of the first year of treatment, 97% of patients in the imatinib group had not experienced a recurrence, compared with 83% in the placebo group. The differences were most notable in patients with tumours larger than 10 cm. No differences in the overall survival rates were noted with this short follow-up. Based on the findings, the study was stopped early and the patients on the placebo arm were allowed to cross over to use imatinib. This study would have major implications in the management of this rather rare tumour.

GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme (GBM) is one of the commonest brain tumours in adults and is associated with poor survival rates. The conventional treatment has been resection followed by radiotherapy. Recently, two studies have shown for the first time that additional use of temozolamide, an alkylating agent, together with radiotherapy and subsequently for another 6 months after resection of GBM, can prolong the OS. The first study showed that patients with previously untreated GBM who received temozolamide with radiotherapy had a median survival of 14.6 months compared to 12.1 months for patients who received radiotherapy alone.[24] The difference was more apparent after two years, when more than twice as many patients in the temozolamide group were still alive. A separate study of these patients found that those who benefited from temozolamide were more likely to have a particular genetic marker in their tumour cells. Patients with this marker (an alteration of the MGMT gene) who received temozolamide plus radiation lived 21.7 months, compared with 15.3 months among those who received radiation alone[25]

HEAD AND NECK CANCER

Until recently, the standard of care for the squamous cell cancers of the head and neck region has been either curative resection, or radiotherapy, or resection followed by adjuvant radiotherapy; however, most of the patients still relapse loco-regionally. The addition of chemotherapy has little or no benefit. More recently, the addition of cetuximab to radiotherapy

Table 3: ***Randomised trials in metastatic renal cell carcinoma***

Study	No of patients	Treatment	ORR	PFS	*p*-value
Motzer	375	IFN-α	6%	5	
	375	Sunitinib	31%	11	<0.001
Escudier*	451	Placebo	37%	2.8	
	452	Sorafenib	62%**	5.5	<0.001
Hudes	207	IFN-α	4.8%	3.1	
	209	Temsiroimus	8.6%	5.5	<0.008
	210	IFN+Temsirolimus	8.1%	4.7	
Escudier	324	IFN-α	12.4%	5.4	
	325	Bevacizumab+IFN-α	10.2	10.2	<0.0001

ORR = Overall reponse rates; TTP = Time to progression; IFN-α = Interferon –α.

* Second line treatment, ** Disease control rate (complete response + partial response + stable disease)

was shown to improve OS for patients with head and neck cancers. Cetuximab, a monoclonal antibody that targets the EGFR in cancer cells, had previously been approved for use in colorectal cancers. The PFS was significantly longer in the cetuximab group: 24.4 versus 14.9 months.[26] The OS in the cetuximab group was also significantly longer: 49 versus 29.3 months. Also, patients with locally advanced hypopharyngeal or laryngeal cancer who received cetuximab with radiation therapy were more likely to have their larynxes preserved compared with patients who received radiation therapy alone.[27] The addition of cetuximab produced relatively mild side effects, including an acne-like rash and local reactions to the drug infusion

Also recently, data demonstrated that adding cetuximab to standard chemotherapy for head and neck cancers increases survival. Data from four clinical trials confirmed that cetuximab also may prolong OS in patients with recurrent head and neck cancers; the difference was statistically significant: the OS was 5.9 months for those who received cetuximab compared with 3.4 months for patients who did not.[28] Following publication of these studies, the FDA this year approved the drug for use in combination with radiation therapy to treat squamous cell cancer of the head and neck, making it the first drug to be approved for this disease in 45 years.

HEPATOCELLULAR CARCINOMA

Hepatocellular Carcinoma (HCC) is the third leading cause of cancer death globally, often resulting in death within a year of diagnosis, and is one of the most difficult cancers to treat. More than 90% of the patients present at a stage where curative treatment with either resection or transplantation is not feasible. For the past 30 years and more, several agents, including chemotherapeutic agents, have been tried, tested, and found to be ineffective. At the American Society of Clinical Oncology (ASCO) meeting in 2008, results of a Phase III trial were presented. Patients who were treated with a multi-kinase inhibitor, sorafenib, had a median survival of 10.7 months, compared to 7.9 months for those who received a placebo.[29] Time to cancer progression was also significantly longer in the treatment group: 5.5 versus 2.8 months. Sorafenib is also approved for treating advanced kidney cancer. The study was terminated early due to the positive results, and represents a one of a kind study where a survival benefit led to rapid approval by the FDA.

LUNG CANCER

Chemotherapy has been shown to improve survival in a select group of patients with non-small cell lung cancer (NSCLC), and is currently considered the standard of care for patients with Stage IIIB and IV disease with a good performance status; however, until now, questions persisted about the benefit of adjuvant chemotherapy. The National Cancer Institute of Canada Clini-

cal Trials Group and the U.S. National Cancer Institute Intergroup Trial found that OS among those patients with early-stage NSCLC who received adjuvant chemotherapy with vinorelbine and cisplatin after surgery was 94 months, compared to 73 months for patients who did not.[30] Five-year survival was also higher in the chemotherapy group (69% versus 54%), and the risk of recurrence was 40% lower in the chemotherapy group. These findings, together with those reported recently by the Adjuvant Navelbine International Trialist Association (ANITA) and the Cancer and Leukemia Group B (CALGB), confirm that adjuvant chemotherapy has a significant role in the treatment of patients with operable NSCLC.[31, 32] These studies resolve a long-standing debate about the benefit of adjuvant chemotherapy, definitively demonstrating that such treatment has a beneficial role in the care of patients with operable NSCLC.

MULTIPLE MYELOMA

Multiple myeloma (MM) was considered to be an incurable B-cell neoplasm. For the first time in several years, use of two new classes of drugs, immunomodulatory (thalidomide and lenalidomide) and proteosome inhibitors (bortezomib) have been considered as major therapeutic advances in the treatment of MM. Previously, thalidomide had been shown to improve the response rate and survival when used in combination with melphalan and prednisolone, and had become an integral part in the management of MM; however, the drug is not free of side-effects. More recently, the effectiveness of lenalidomide has been demonstrated in Phase III clinical trials.[33, 34] Patients with relapsed/refractory MM were randomised to lenalidomide plus dexamethasone or dexamethasone alone. Patients in the lenalidomide group had superior response rates and duration of response. Lenalidomide is an analogue of thalidomide, and works by inhibiting angiogenesis and immune modulation, and increasing apoptosis. Lenalidomide is generally better tolerated than thalidomide. The proteosome inhibitor bortezomib is another recent addition to the MM treatment armamentarium. The target of bortezomib is the 26S proteasome. The benefit of bortezomib was shown in the Phase III APEX trial. Patients with relapsed/refractory MM were randomised to receive bortezomib or dexamethasone[35]. The response rate, median time to progression, and 1-year survival were significantly increased in the bortezomib group. In addition, clinical trials have further established the role of stem cell transplantation and the benefits of post-transplant maintenance therapy. These advances have resulted not only in expanded treatment options, but seem to have changed the natural history of MM which was once considered to be an incurable neoplasm.

NON-HODGKIN'S LYMPHOMA

Follicular lymphoma (FL) is an indolent form of non-Hodgkin's lymphoma (NHL), the outcomes of which had not improved over the past 3 decades.[36] In the last 3 years, four large scale randomized trials have shown that adding the anti-CD20 monoclonal antibody, rituximab, to conventional combination chemotherapies improves the PFS and the OS.[37-40] Rituximab added to a combination of cyclophosphamide, vincristine, prednisolone (CVP); cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP); mitoxantrone, cyclophosphamide, prednisolone (MCP) or chlorambucil, vincristine, prednisolone with interferon maintenance (CHVP-IFN-α), brought clear survival advantage (see Table 2 for details). A combination of rituximab and chemotherapy has now become the standard of care in the treatment of the commonest form of indolent lymphoma, the FL.[41, 42]

Furthermore, another series of studies have established the successful role of rituximab for maintenance after completion of chemotherapy.[43-45] Used in this way, PFS and OS rates are prolonged. For example, in one study, 56% of patients who received maintenance rituximab showed no progression, compared with 33% of patients who were observed following chemotherapy. Moreover, 88% of the rituximab group was still alive after 4 years, compared with 72% of the observation group

In a different setting, radioactivity conjugated with the anti-CD antibody has shown to induce higher remission rate, prolong the PFS and the OS. Two agents, ^{90}Y and ^{131}I have been extensively studied and the results have been reported. Increasingly, the radioimmuno-labelled antibodies are being incorporated in the management of indolent lymphomas not only after relapsed FL, but also in first line therapy.[46, 47]

As a result of recent developments, not only rituximab and radiolabelled antibodies have become the standard of care in the management of FL, but also, for the first time in the last three decades, the natural history of the disease seems to be changing, with the hope of a cure.

Table 2: ***Randomised trials comparing standard chemotherapy with standard chemotherapy and rituximab for non-Hodgkins lymphoma***

Study	No. of patients	Treatment	TTP	*p*-value OS	*p*-value	
Solal-Celingy	159	CVP	14		81%*	
	162	R-CVP	34	<0.0001	89%	=0.053
Hiddeman	205	CHOP	29		90%**	
	223	R-CHOP	NR	<0.001	95%	=0.016
Herold	96	MCP	25		74%	
	105	R-MCP	54	<0.0001	88%	=0.014
Salles	175	CHVP-IFN	62%***		n/a	
	184	R-CHVP-IFN	78%	<0.03	n/a	

TTP = Time to progression; OS = Overall survival; CVP = cyclophosphamide, vincristine, prednisolone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; MCP = mitoxantrone, cyclophosphamide, prednisolone; R- MCP = rituximab, mitoxantrone, cyclophosphamide, prednisolone; CHVP-IFN = chlorambucil, vincristine, prednisolone, interferon α; R- CHVP-IFN = rituximab, chlorambucil, vincristine, prednisolone, .interferon α; *3 year survival; **2 year survival; ***Event-free survival

OVARIAN CANCER

The vast majority of patients with epithelial ovarian cancer present with advanced stage disease, and the standard of care is debulking surgery followed by adjuvant systemic chemotherapy. Despite the treatment, more than 80-90% of the patients relapse and die of their disease within few years of diagnosis. Continued attempts to improve the survival rates have been unsuccessful in the past 10 years, since adjuvant chemotherapy with a combination of platinum with paclitaxel emerged as the standard of care.[48] However, recently, the results of a Phase III trial including 415 patients with advanced ovarian cancer revealed that intra-peritoneal administration of chemotherapy extended the median survival by more than 1 year (49.7 months versus 65.6 months) compared with intravenous chemotherapy.[49] Patients with Stage III ovarian cancer were randomly assigned to either intravenous paclitaxel plus cisplatin or intravenous paclitaxel plus intra-peritoneal cisplatin and paclitaxel.

However, patients who received intra-peritoneal therapy experienced more toxic side effects, and were more likely to report poorer quality of life, compared with women who received intravenous therapy. Only 42% of women in the intra-peritoneal chemotherapy group were able to complete all six cycles of therapy, compared with 83% of those who received intravenous chemotherapy.[50] Such toxicity has limited the widespread use of intra-peritoneal therapy.

PANCREATIC CANCER

Patients with advanced pancreatic cancer have a poor prognosis and the standard of care for the past 12 years has been the use of single agent gemcitabine. Several attempts to use combinations, such as with cisplatin, oxaliplatin, capecitabine and 5-FU have not yielded encouraging results. Pancreatic cancers are known to over-express EGFR and recently a tyrosine kinase inhibitor of the EGFR, erlotinib, was used in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer.[51] A total of 569 patients were randomly assigned to receive either gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus a placebo in a double-blind, international Phase III trial. One-year survival was also greater with erlotinib plus gemcitabine (23% versus 17%). PFS was significantly longer with erlotinib plus gemcitabine. For the first time, a combination has been found to be superior than the single agent chemotherapy; however, given the modest gain in survival, pending complementary studies, the addition of erlotinib can not still be considered the standard of care. Nonetheless, this study paves the way for further trials employing signal transduction inhibitors in the management of unresectable pancreatic cancer.

PROSTATE CANCER

Prostate cancer is one of the most common cancers in men in the western world. Effective screening using digital rectal examination (DRE), and serum estima-

Table 3: ***Randomised trials in metastatic renal cell carcinoma***

Study	No of patients	Treatment	ORR	PFS	*p*-value
Motzer	375	IFN-α	6%	5	
	375	Sunitinib	31%	11	<0.001
Escudier*	451	Placebo	37%	2.8	
	452	Sorafenib	62%**	5.5	<0.001
Hudes	207	IFN-α	4.8%	3.1	
	209	Temsiroimus	8.6%	5.5	<0.008
	210	IFN+Temsirolimus	8.1%	4.7	
Escudier	324	IFN-α	12.4%	5.4	
	325	Bevacizumab+IFN-α	10.2	10.2	<0.0001

ORR = Overall reponse rates; TTP = Time to progression; IFN-α = Interferon –α.

* Second line treatment, ** Disease control rate (complete response + partial response + stable disease)

tion of the prostate specific antigen (PSA) means that more patients are being diagnosed at an early stage. However, since the majority of patients is diagnosed at an old age and has a higher chance of dying because of the cancer-unrelated causes, an expectant approach or 'watchful waiting' has been employed as a method of early treatment. As yet there is no clear understanding as to which patients require aggressive treatment. A total of 695 men with early prostate cancer were randomly assigned to radical prostatectomy (347 men) or 'watchful waiting' (348 men).[52] During a median of 8.2 years of follow-up, 83 men in the surgery group and 106 men in the watchful-waiting group died. Radical prostatectomy was found to have reduced the disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 years was small, but the reductions in the risks of metastasis and local tumour progression were substantial. When analysed by age, the benefits of surgery were greatest among younger men: among men under age 65, 19.2% in the 'watchful waiting' group had died after 10 years compared with 8.5% of those who had surgery, while among men age 65 and older, 11.5% in the 'watchful waiting' group died versus 8.5% of those in the surgery group. Based on these data, men under age 65 who have early-stage prostate cancer should undergo surgery to remove the prostate, while older men may choose 'watchful waiting'.

RENAL CELL CARCINOMA

Nearly one-half of patients with renal cell carcinoma (RCC) have metastatic disease at the time of initial presentation. The tumour is not sensitive to chemotherapy, and the options included treatment with interferon-α (IFN-α) or interleukin-2 (IL-2) or surgical resection of metastases. However, response rates to the cytokine treatment do not exceed 10-20%, and the long-term prognosis remains dismal. High-dose IL-2, approved for treatment of advanced RCC, has significant limitations. The treatment must usually be administered in an intensive care unit, is associated with significant toxicity, and has not demonstrated a survival benefit. Over the past two years, four different agents have been proved to be effective in inducing responses, with the possibility of some longer remissions. Sunitinib, sorafenib, temsirolimus, and bevacizumab have demonstrated significant efficacy in clinical trials and have been approved by the FDA for the treatment of advanced RCC [Table 3].[53-56]

Ever since the recognition that the tumour-suppressor von Hippel-Lindau (VHL) gene is mutated in most clear-cell carcinomas, resulting in angiogenesis and cell growth, a number of targeted therapies that block the downstream effects of the mutated gene have been developed. Sunitinib and sorafenib, for example, inhibit multiple receptor tyrosine kinases. Temsirolimus inhibits mTOR, which functions as an intermediary in a variety of cell signalling events to regulate cell growth and proliferation as well as angiogenesis and cell survival. Bevacizumab binds to VEGF and inhibits angiogenesis.

In the first study, a total of 750 patients with a good performance status and good- and intermediate-risk clear cell RCC were randomized to receive either sunitinib or IFN α. The median PFS was 11 months for

the sunitinib arm and 5 months for the IFN α arm ($p < 0.000001$).[53] In an another study, 905 patients who had failed one prior systemic therapy in the last 8 months and had measurable disease, clear cell histology, a good or intermediate prognosis, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 were randomised to receive either sorafenib or placebo. Sorafenib significantly prolonged median PFS compared with placebo (24 vs 12 weeks, $p < 0.000001$).[54] In a different study, 626 patients with several poor-risk features were randomised to receive either IFN α, temsirolimus or a combination of temsirolimus plus IFN α. The median survival of patients was superior in the temsirolimus-alone arm compared with IFN α (10.9 versus 7.3 months, $p < 0.007$), while the combination arm was not superior to IFN α (8.4 months, $p = 0.69$). The median PFS was statistically superior for both temsirolimus arms (3.7 months) compared with IFN α (1.9 months).[55] In the fourth study, patients with metastatic kidney cancer who had undergone nephrectomy were randomly assigned to receive either bevacizumab or a placebo in addition to interferon. Adding bevacizumab nearly doubled PFS, from 5.4 months to 10.2 months. The tumour response rate was 31% for the bevacizumab group versus 13% for the placebo group.[56]

Over the past 2 years, the use of these agents has essentially replaced the standard cytokine treatment, which had been the standard of care for more than two decades.

CONCLUSION

Oncology treatment has begun to progress by quantum leaps. A glance at this review would suggest that whereas, in some areas, a paradigm of management has shifted, for example, the use of targeted therapy in the adjuvant treatment of breast cancer, and the use of monoclonal antibody together with chemotherapy in indolent lymphoma, resulting in the cure of many more patients than were seen in the very recent past, in other areas, new treatments have emerged, in hard-to-treat cancers, such as, HCC and RCC, offering hope of a meaningful prolongation of life to thousands of patients annually. The improved survival seen with the addition of targeted therapies as well as chemotherapeutic agents in cancers of the colon, head and neck, NSCLC, and the pancreas represents the continual improvement seen using the Phase III randomised trials.

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