Maintenance therapy in solid tumors

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The concept of maintenance therapy has been well studied in hematologic malignancies, and now, an increasing number of clinical trials explore the role of maintenance therapy in solid cancers. Both biological and lower-intensity chemotherapeutic agents are currently being evaluated as maintenance therapy. However, despite the increase in research in this area, there has not been consensus about the definition and timing of maintenance therapy. In this review, we will focus on continuation maintenance therapy and switch maintenance therapy in patients with metastatic solid tumors who have achieved stable disease, partial response, or complete response after first-line treatment.

Maintenance therapy is the subject of an increased interest in cancer research. In contrast to conventional chemotherapy that aims to kill as many cancer cells as possible, the goal of treatment with maintenance therapy is to sustain a stable tumor mass, reduce cancer-related symptoms, and prolong the time to progression and the related symptoms. A therapeutic strategy that is explicitly designed to maintain a stable, tolerable tumor volume could increase a patient's survival by allowing sensitive cells to suppress the growth of resistant cells.[1] Maintenance therapy has been well studied in hematologic malignancies, and a growing number of clinical trials are exploring the role of maintenance therapy in solid cancers.

Optimal agents for maintenance therapy should be easy to administer, be associated with an acceptable toxicity profile, and be cost effective. Both the immediate and cumulative side effects of the agent should be taken into consideration. Biologic agents are good candidates for treatment in the setting of maintenance therapy, and a variety of these agents is becoming available now that more is known about the growth and microenvironment of tumors. Such agents would include those that target epidermal growth factor receptors (EGFRs) such as erlotinib, gefitinib, and cetuximab; vascular endothelial growth factor (VEGF) receptors such as bevacizumab; and tumor-associated antigens such as oregovomab and abagovomab, which target CA 125 (cancer antigen 125). Both biologic and lower intensity chemotherapeutic agents, such as capecitabine and oral 5-fluorouracil (5-FU), are currently being evaluated as maintenance therapy.

Despite the increase in research in this area, there is no consensus on the definition and timing of maintenance therapy. The term maintenance therapy is used in a variety of treatment situations, such as prolonged first-line therapy and less-intense or different therapy given after first-line therapy. The National Comprehensive Cancer Network (NCCN) recently defined two maintenance strategies in the setting of non–small cell lung cancer:[2] continuation maintenance therapy (defined as the administration of a lower intensity version of the first-line regimen), and switch maintenance therapy (defined as the administration of a different agent after completion of the first-line regimen). We propose to use these terms in all solid tumor research (Table 1).

Non–small cell lung cancer

Maintenance therapy in advanced non−small cell lung cancer (NSCLC) is an established concept, as evidenced by the NCCN's incorporation of recommendations for maintenance therapy into its 2011 guidelines.[2] Currently, there is evidence that maintenance therapy with pemetrexed, gemcitabine, docetaxel, and erlotinib (with or without gemcitabine or bevacizumab) improves progression-free survival (PFS) and/or overall survival (OS), as discussed infra (Table 2).

Pemetrexed

Pemetrexed is a cytotoxic agent that has been extensively studied as a maintenance therapy in

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TABLE 1 Working definitions of types of maintenance therapy

Term	Working definition	Examples
Continuation therapy	Administration of the first-line regimen until disease progression or for a defined number of cycles beyond the standard duration	Hormone therapy in breast cancer
Continuation maintenance therapy[2]	Administration of a lower intensity version of the first-line regimen	Leucovorin plus fluorouracil in patients with advanced colorectal carcinoma with stable disease or better after FOLFOX7 chemotherapy.
Switch maintenance therapy[2]	Administration of a different agent after completion of the first-line regimen	Pemetrexed in patients with advanced non–small cell lung cancer achieving stable disease or better after 4 cycles of platinum-based chemotherapy.

Abbreviation: FOLFOX7, combined leucovorin, fluorouracil, plus oxaliplatin.

TABLE 2 Phase 3 trials with regimens that significantly improved TTP, PFS, and/or OS

Disease	Agent (control)	Type of maintenance therapy	Effect on TTP, PFS, or OS
NSCLC	Pemetrexed[3] (placebo)	Switch	PFS, 4.3 mo (95% CI, 4.1-4.7) vs 2.6 mo (95% CI, 1.7-2.8), respectively; HR, 0.50; 95% CI, 0.42-0.61; $P < .0001$ OS, 13.4 mo (95% CI, 11.9-15.9) vs 10.6 mo (95% CI, 8.7-12.0); HR, 0.79; 95% CI, 0.65-0.95; $P = .012$
	Erlotinib[12] (placebo)	Switch	PFS, 12.3 wk vs 11.1 wk, respectively (HR, 0.71; 95% CI, 0.62-0.82; $P < .0001$) OS, 12 mo vs 11 mo (HR, 0.81; 95% CI, 0.70-0.95; $P = .0088$)
	Gemcitabine[5] (BSC alone)	Continuation	TTP, 6.6 mo vs 5.0 mo, respectively ($P < .001$)
	Docetaxel[8] (immediate vs delayed)	Switch	PFS, 5.7 mo vs 2.7 mo, respectively ($P = .0001$)
	Gemcitabine or erlotinib[16] (observation)	Gemcitabine as continuation; erlotinib as switch	PFS, observation/gemcitabine/erlotinib, 2.1, 3.7, 2.8 mo, respectively. HR erlotinib by independent review, 0.83; 95% CI, 0.73-0.94; HR gemcitabine, 0.51; 95% CI, 0.39-0.66.
	Bevacizumab plus erlotinib[14] or bevacizumab plus placebo)	Bevacizumab as continuation; erlotinib as switch	PFS, 4.8 mo vs 3.7 mo, respectively (HR, 0.722; 95% CI, 0.592-0.881; $P = .0012$)
Colorectal cancer	Leucovorin and fluorouracil[34] (chemotherapy discontinuation)	Continuation	PFS, 8.6 mo vs 6.6 mo, respectively (HR, 0.61; $P = .0017$)
Ovarian cancer	Paclitaxel[45,46,a] (12 or 3 cycles)	Continuation	PFS, 24 mo vs 12 mo, respectively ($P = .016$)[46] OS, 80 mo vs 38 mo ($P = .012$) [46]
Breast cancer	Pegylated liposomal doxorubicin[58] (observation)	Switch	TTP, 8.4 mo vs 5.1 mo (HR, 0.54; 95% CI, 0.39-0.76; $P = .0002$)

Abbreviations: BSC, best supportive care; HR, hazard ratio; mo, months; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; TTP, time to progression; wk, week.
[a] Another phase 3 trial failed to show any difference.

advanced NSLC. In a recent phase 3 trial, 663 patients who had not progressed on 4 cycles of platinum-based chemotherapy were randomized to switch maintenance therapy with pemetrexed or placebo plus best supportive care (BSC). Pemetrexed significantly improved PFS, compared with placebo (4.3 months [95% confidence interval, CI, 4.1-4.7] vs 2.6 months [95% CI, 1.7-2.8], respectively; hazard ratio [HR], 0.50; 95% CI, 0.42-0.61; $P < .0001$) and OS (13.4 months [95% CI, 11.9-15.9] vs 10.6 months [95% CI, 8.7-12.0]; HR, 0.79; 95% CI, 0.65-0.95; $P = .012$).[3] Another randomized, phase 3 trial that compared pemetrexed plus BSC vs placebo plus BSC

in patients who did not progress after 4 cycles of pemetrexed and cisplatin is ongoing.[4]

Other chemotherapeutic agents

A phase 3 study showed improved time to progression (TTP) with gemcitabine maintenance compared with BSC after first-line gemcitabine plus cisplatin (6.6 vs 5.0 months, respectively; $P < .001$), but it did not show benefit in OS (13.0 vs 11.0 months; $P = .195$).[5] A second phase 3 study with gemcitabine plus BSC vs BSC alone as maintenance therapy, also after the standard gemcitabine-carboplatin combination, failed to show a difference in TTP or OS (8.0 vs 9.3 months, respectively; $P = .84$).[6] Continuation maintenance therapy in a phase 3 trial with paclitaxel or observation seemed to delay the TTP (38 vs 29 weeks, respectively) and yield a greater median survival time (75 vs 60 weeks), but the sample size was small (65 patients in each group) and there were no significant differences.[7] A phase 3 trial that compared immediate with delayed docetaxel after front-line gemcitabine plus carboplatin also failed to improve OS (12.3 vs 9.7 months, respectively; $P = .0853$), but showed an improvement in PFS (5.7 vs 2.7 months; $P = .0001$).[8] Switch maintenance carboxyaminoimidazole after any first-line treatment proved unsuccessful (OS, 11.4 vs 10.5 months, respectively, log rank $P = .54$; median TTP, 2.8 vs 2.4 months, log rank $P = .50$),[9] as did switch maintenance vinorelbine after mitomycin, ifosfamide, and cisplatin (1- and 2-year survival of 42.2% and 20.1% vs 50.6% and 20.2%, respectively; $P = .48$).[10]

Erlotinib

The role of erlotinib and gefitinib in maintenance therapy has been studied in several large, randomized clinical trials. The addition of erlotinib to gemcitabine plus either cisplatin or carboplatin showed promise in the FAST ACT trial, in which a statistically significant improvement in PFS ($P = .005$) was observed in the erlotinib arm.[11] In the SATURN trial, 884 patients with nonprogressive disease after first-line platinum doublet chemotherapy were treated with erlotinib or placebo. The median PFS was 12.3 and 11.1 weeks, respectively (HR, 0.71; 95% CI, 0.62-0.82; $P < .0001$), and OS was 12 and 11 months (HR, 0.81; 95% CI, 0·70-0·95; $P = .0088$).[12] The potential of combining bevacizumab with erlotinib was first demonstrated in the BETA trial (erlotinib with and without bevacizumab in patients with advanced NSCLC who were not responding to standard first-line chemotherapy), in which PFS was improved in patients treated with both drugs (3.4 vs 1.7 months, respectively; HR, 0.62; $P < .0001$).[13] In the ATLAS trial, 768 patients, who did not progress after 4 cycles of bevacizumab with platinum-based doublet chemotherapy, were randomized to either bevacizumab plus erlotinib or to bevacizumab plus placebo. The median PFS was 4.8 vs 3.7 months, respectively (HR, 0.722; 95% CI, 0.592-0.881; $P = .0012$). There was no significant difference in OS, although the study was not powered to detect OS difference (15.9 vs 13.9 months; HR, 0.90; 95% CI, 0.74-1.09; $P = .2686$).[14,15] In the IFCT-GFPC 0502 trial, 464 patients who did not progress after 4 cycles of cisplatin plus gemcitabine were randomized to observation, gemcitabine, or erlotinib. The median PFS by investigator assessment was 2.1, 3.7, or 2.8 months, respectively. PFS by independent review (83% patients assessed) was significantly prolonged by gemcitabine (HR, 0.51; 95% CI, 0.39-0.66) and by erlotinib (HR, 0.83; 95% CI, 0.73-0.94), compared with placebo.[16]

Gefitinib

The role of gefitinib as maintenance therapy is controversial, with several trials showing contradicting results. The EORTC trial 08021 evaluated the role of gefitinib, compared with placebo, in 173 patients without progressive disease after 4 cycles of platinum-based chemotherapy. The trial was prematurely closed to entry because of low accrual. The difference in PFS was significant (4.1 vs 2.9 months, respectively; HR, 0.61; 95% CI, 0.45-0.83; $P = .0015$), but the difference in OS in was not significant (10.9 vs 9.4 months; HR, 0.83; 95% CI, 0.60-1.15; $P = .2$).[17] In the SWOG S0023 trial, 243 patients with advanced NSCLC who did not progress after 2 cycles of cisplatin, etoposide, and thoracic radiation followed by 3 cycles of docetaxel were randomized to maintenance gefitinib or placebo. After a median follow-up of 27 months, the median OS was 23 months in patients in the gefitinib arm, compared with 35.0 months for those receiving placebo (2-sided $P = .013$; HR, 0.633; 95% CI, 0.44-0.91). The reason for this unexpected decreased survival in patients treated with gefitinib was not clear.[18]

Cetuximab

The role of maintenance cetuximab is not clear at this time. In the FLEX trial, patients with EGFR-expressing stage IIIB or IV NSCLC received cisplatin and vinorelbine with or without cetuximab. Patients in the cetuximab group received continuation maintenance cetuximab until disease progression or unacceptable toxicity. Overall, cetuximab improved survival (median, 11.3 vs 10.1 months, respectively; HR for death, 0.871; 95% CI, 0.762-0.996; $P = .044$), but the effect of the maintenance alone was not separately studied.[19]

Immunotherapy

Maintenance immunotherapy has shown promise in several smaller trials. In a phase 2 trial, 38 patients with advanced NSCLC who had not progressed after cisplatin and vinorelbine and who had a median serum VEGF level of 508 ng/mL were treated with subcutaneous interleukin-2 (IL-2) and oral 13-cis retinoic acid (RA) and compared with matched controls. The median PFS was 16.5 and 8.4, respectively (P = .0003), and OS was 17.80 and 11.8 months (log rank test, P =.0364).[20] In a randomized phase 2 trial, patients who were not progressing after chemotherapy (platinum-based for 165 of 171 patients) were randomized to BLP25 liposome vaccine (L-BLP25) plus BSC or to BSC alone. The median OS was 17.4 and 13 months, respectively (P = .066). In the subgroup of patients with stage IIIB locoregional disease, the median survival time for the L-BLP25 arm had not yet been reached, compared with 13.3 months for the BSC arm (adjusted HR, 0.524; 95% CI, 0.261-1.052; P = .069).[21]

Small cell lung cancer

Maintenance therapy in patients with extensive-stage small cell lung cancer (SCLC) is not yet an established concept. Few trials have been published recently to evaluate the role of maintenance chemotherapy in SLCL, and of those, thalidomide was found to increase OS in 1 trial, but only in a subgroup of patients who had good performance status. Other agents have not been proved successful in SCLC.

Chemotherapy

In 2005, a meta-analysis of trials conducted in the 1980s and 1990s concluded that maintenance chemotherapy in SCLC improved survival, although there were no conclusions about who should be treated and what treatment should be used.[22] In a more recent randomized trial, 45 patients with complete response or partial response after irinotecan plus cisplatin were randomized to irinotecan or observation. There were no significant differences between the 2 groups in PFS (12 vs 9.9 months, respectively) or OS (17.6 vs 20.5 months).[23]

Thalidomide

Thalidomide has been evaluated as maintenance therapy in several trials. In a phase 2 trial, 30 patients who were not progressing after first-line chemotherapy (carboplatin or cisplatin with either etoposide or irinotecan) were treated with thalidomide. The median survival from initiation of induction chemotherapy was 12.8 months (95% CI, 10.1-15.8 months), although median duration on thalidomide was only 79 days.[24] In a phase 3 trial, 92 patients who had responded to etoposide, cisplatin, cyclophosphamide, and 4'-epidoxorubicin were given 2 additional cycles of chemotherapy and randomized to thalidomide or placebo for up to 2 years. A nonsignificant increase in OS was found in the thalidomide group (11.7 vs 8.7 months, respectively; HR, 0.74; 95% CI, 0.49-1.12; P = .16). However, in a subgroup of patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 1 or 2, those who received thalidomide had a significantly longer survival (HR, 0.59; 95% CI, 0.37-0.92; P = .02). The disease also progressed more slowly in the thalidomide patients (HR, 0.54; 95% CI, 0.36-0.87; P = .02), although the difference did not reach statistical significance for the whole population (HR, 0.74; 95% CI, 0.49-1.12; P = .15).[25]

Other agents

Among the other agents that have been evaluated as maintenance therapy in extensive-stage SCLC but have not shown improvement in PFS or OS are interferon (IFN)–alfa with RA and trophosphamide;[26] marimastat compared with placebo (OS, 9.3 vs 9.7 months, respectively; P = .90; PFS, 4.3 vs 4.4 months, P = .81);[27] imatinib (PFS, 1.3 months);[28] and vandetanib compared with placebo (PFS, 2.7 vs 2.8 months; OS, 10.6 vs 11.9 months).[29]

Malignant pleural mesothelioma

In patients with malignant mesothelioma, only pemetrexed and IL-2 have been evaluated in the setting of maintenance therapy. Both therapies have shown promise in phase 2 trials, but randomized controlled trials need to be done to determine their role.

Pemetrexed

In a phase 2 trial, 13 patients who responded to pemetrexed with or without carboplatin were treated with maintenance pemetrexed. Although the study was not randomized or designed to demonstrate improvements in TTP and OS, patients who received maintenance had an almost threefold longer TTP and OS than did those who did not receive maintenance therapy (OS, 17.9 vs 6 months, respectively; PFS, 8.5 vs 3.4 months; P < .0001).[30]

Interleukin-2

IL-2 has been used in a phase 2 trial as maintenance therapy in patients who responded to epirubicin plus gemcitabine.[31] In all, 32% of patients survived for 1 year, 11% survived for 2 years, and 4% survived for 3 and 4 years. TTP was 58 weeks, and survival was 63.5 weeks. Although the role of IL-2 as maintenance therapy seemed encouraging, that was not a primary end point of the study.

Colorectal carcinoma

The concept of maintenance therapy in metastatic colorectal cancer (MCC) has been tested in several large randomized trials, some of which are discussed infra. Only continuation maintenance with leucovorin plus fluorouracil has been found to increase PFS in a phase 3 trial (Table 2). However, several other agents appear to be promising candidates after being evaluated in phase 2 trials.

Leucovorin plus fluorouracil

First, a large, randomized trial showed that a complete break in therapy was feasible after treatment with leucovorin plus fluorouracil (OS HR, 0.87 favoring intermittent therapy; 95% CI, 0.69-1.09; $P = .23$).[32] Then the OPTIMOX-1 trial compared maintenance with leucovorin plus fluorouracil after FOLFOX7 (combined leucovorin, fluorouracil, plus oxaliplatin) with continuation therapy with FOLFOX4.[33] The results for FOLFOX4 and FOLFOX7 were similar in terms of PFS (9.0 vs 8.7 months, respectively), OS (19.3 vs 21.2 months), and response rates (58.5% vs 59.2%), with a statistically significant reduction in the major grade of neurotoxicity (17.9% in the continuous arm vs 13.3% in the maintenance arm; $P = .12$), indicating that oxaliplatin can be stopped after 6 preplanned cycles and that a maintenance therapy is a feasible option. The OPTIMOX-2 trial compared a modified FOLFOX7 induction followed by continuation maintenance with combined leucovorin plus fluorouracil, with induction therapy followed by a chemotherapy-free period until progression.[34] This trial confirmed the need for maintenance therapy. A chemotherapy-free interval shortened the duration of disease control (9.2 vs 13.1 months, respectively; $P = .046$) and PFS (6.6 vs 8.6 months; HR, 0.61; $P = .0017$). However, there was no difference in OS (23.8 vs 19.5 months; HR, 0.88; $P = .42$).

Capecitabine

In a phase 2 trial, 28 patients with MCC who did not progress on FOLFOX4 therapy were treated with switch maintenance capecitabine.[35] The median response duration (9.2 months) and PFS (8.6 months) were comparable with those usually reported in the treatment of MCC patients. However, only 28 patients were evaluated, so no firm conclusions can be drawn from this study. Several phase 2 trials have evaluated capecitabine plus oxaliplatin therapy (XELOX), and continued capecitabine as maintenance therapy until progression in patients with stable disease (SD), partial response (PR), or complete response (CR). Both trials showed promising results, but were not set up to evaluate the effect of maintenance therapy alone.[36,37]

Oral uracil-tegafur

Maintenance uracil-tegafur (UFT) was given until disease progression to 22 patients who did not progress after a 6-month FOLFOX4 regimen in a single-arm, phase II trial.[38] The median time to progression was 13.9 months (interquartile range, 7.7-20.1) and the median survival time was 31 months (range, 20-31 months). An evaluation of quality of life demonstrated a trend toward better quality of life during UFT treatment, which supported the feasibility of UFT as a more easily administered maintenance therapy.

Bevacizumab

In the MACRO/TTD trial, patients who responded after 6 cycles of XELOX plus bevacizumab were randomized to continue that regimen or to receive bevacizumab only until progression. The results were similar for PFS (11 vs 10.3 months, respectively) and OS (25.3 vs 20.7 months), which suggested that maintenance with bevacizumab is not detrimental, compared with a continuous treatment with both XELOX and bevacizumab.[39]

Immunotherapy

Maintenance immunotherapy with IL-2 with RA has been evaluated in a phase 2 trial in 40 patients with metastatic colorectal cancer who responded to oxaliplatin fractionated over 2 consecutive days, followed by leucovorin bolus and 5-FU continuous infusion. Both median PFS (27.8 vs 12.5 months, respectively; $P \leq .0001$) and OS (52.9 vs 20.2 months; $P < .0001$) improved, compared with a historical control group.[40]

Ongoing trials

Ongoing trials include the CAIRO 3 trial (www.dccg.nl/trials/cairo3; maintenance capecitabine plus bevacizumab), the Swiss-SAKK 41/06 trial (NCT00544700; maintenance bevacizumab), the German Arbeitsgemeinschaft für Internistische Onkologie (AIO)KRK 0207 trial (NCT00973609; maintenance fluoropyrimidine and bevacizumab), the GERCOR (French Oncology Research Group)–C04-2 trial (NCT00265824; maintenance bevacizumab and erlotinib), and the SICOG (Southern Italy Cooperative Oncology Group) MARTHA trial (NCT00797485; maintenance bevacizumab).

Other gastrointestinal malignancies

There have been numerous trials that have included maintenance therapy in patients with metastatic esophageal, gastroesophageal junction, gastric carcinoma,

and pancreatic and hepatocellular carcinoma, but none was designed to evaluate the maintenance phase of the trial. Therefore, no conclusions can be drawn about the effect of maintenance therapy on PFS or OS. The agents that were used in those trials include gemcitabine, bevacizumab, doxifluridine, erlotinib, S-1 (combined tegafur, gimeracil, and oteracil), gefitinib, and 5-FU.

Maintenance immunotherapy, however, has been evaluated in a phase 2 trial in which patients with advanced pancreatic and biliary tree adenocarcinoma that had not progressed after 3 courses of cisplatin plus gemcitabine and subsequent radiotherapy with capecitabine received IL-2 with RA. The median PFS was 16.2 months, whereas the median OS had not been reached after a median follow-up of 27.5 months.[41]

Ovarian cancer

The role of maintenance therapy in ovarian cancer is controversial as trials have shown conflicting results. Continuation maintenance therapy with paclitaxel showed improved PFS and OS in a phase 3 trial (see infra; Table 2), but did not show any benefit in another trial. Maintenance therapy with the CA 125 monoclonal antibody oregovomab has so far not shown any benefit. Several other agents (including pegylated liposomal doxorubicin, carboplatin, BIBF 1120 (a triple angiokinase inhibitor), and IL-2 with RA showed promise in smaller phase 2 trials, but randomized trials need to be done to determine their role.

Chemotherapy

Maintenance chemotherapy in advanced ovarian cancer (AOC) has been evaluated in several randomized trials, as well as in a recent meta-analysis. The meta-analysis included 6 randomized controlled trials that evaluated the role of maintenance therapy with platinum agents, doxorubicin, and paclitaxel in patients with epithelial ovarian cancer. In that meta-analysis, there was no significant difference in the 3-, 5- and 10-year OS or PFS.[42] Maintenance paclitaxel was compared with placebo in a phase 3 trial in which 200 patients with AOC in CR after paclitaxel plus platinum-based chemotherapy were included.[43] There was no significant difference between the placebo and paclitaxel arms in 2-year PFS (54% vs 59%, respectively) or OS (90% vs 86%). In a phase 2 trial, 48 patients with microscopic residual disease after 6 cycles of paclitaxel plus platinum-based chemotherapy received weekly paclitaxel for 21 weeks.[44] The 3-year PFS was 18% (95% CI, 9.6%-33.8%), and the 3-year OS was 64% (95% CI, 52.0%-78.0%).

Investigators in a phase 3 trial compared short and long paclitaxel maintenance therapy in 296 patients with AOC or primary carcinoma of the peritoneum in CR after they had received platinum plus paclitaxel-based chemotherapy. The patients were randomized to either 3 or 12 cycles of continuation maintenance paclitaxel every 28 days.[45] The trial was prematurely closed when an interim analysis revealed that, compared with the 3-cycle arm, there was a statistically significant improvement in PFS in the 12-cycle arm (21 vs 28 months, respectively). Updated PFS in 2010 was 12 and 24 months ($P = .016$), and OS was 38 and 80 months ($P = .012$).[46] Pegylated liposomal doxorubicin (PLD) was given to 12 patients with AOC and/or peritoneal cancers with no evidence of disease after platinum plus paclitaxel-based chemotherapy and debulking in a single-arm, phase 2 trial.[47] Median disease-free survival was 10 months (mean, 18 months) and median OS had not yet been reached at the time of reporting. PLD was given as maintenance therapy to 16 patients with AOC and/or fallopian tube cancer who responded to PLD with carboplatin or topotecan doublets or to PLD alone.[48] PFS was 37 months (range, 18-71 months or more). Maintenance carboplatin was given to 22 patients with epithelial ovarian cancer in CR after platinum-based chemotherapy in a single-arm, phase 2 trial.[49] Disease-free survival (36 months) and OS (83 months) were encouraging.

Oregovomab and abagovomab

In an early phase 3 trial, 145 patients with AOC in CR after chemotherapy were randomized to oregovomab or placebo.[50] For the population overall, median time to relapse (TTR) was not different between the treatments, at 13.3 months for oregovomab and 10.3 months for placebo ($P = .71$). However, in an identified subpopulation with favorable prognostic indicators, TTR was 24.0 months in the oregovomab group, compared with 10.8 months for placebo (unadjusted HR, 0.543; 95% CI, 0.287-1.025). The 5-year follow-up results showed median survival times of 57.5 months for oregovomab and 48.6 months for placebo (HR, 0.72; 95% CI, 0.41-1.25).[51] However, for the identified subpopulation, the median survival had not yet been reached. In another trial, 373 patients with AOC and no evidence of disease after carboplatin and paclitaxel were randomized to oregovomab or placebo; no differences in clinical outcomes were seen.[52] Abagovomab is currently being evaluated in a randomized controlled trial in which 888 patients with epithelial ovarian cancer with CR after platinum-taxane–based chemotherapy were randomized to abagovomab or placebo.[53]

Other agents

Other agents evaluated in AOC include BIBF 1120 and tanomastat (a matrix metalloprotease inhibitor). In a randomized, double-blind, phase 2 trial in patients who responded to their last (at least second-line) chemotherapy, 84 patients were randomized to BIBF 1120 or placebo. [54] The 36-week PFS was 15.6% (95% CI, 3.8%-27.3%) for BIBF 1120 and 2.9% (95% CI, 0.0%-8.4%) for placebo. Although the trial was not powered for a direct comparison, the PFS hazard ratio was 0.68 (95% CI, 0.42-1.09); median time to progression was 4.8 months for BIBF 1120 and 2.8 months for placebo. In a phase 3 trial, 243 patients with AOC who responded to 6 to 9 cycles of platinum- and paclitaxel-containing chemotherapy were randomized to tanomastat or observation.[55] There were no significant differences reported in TTP (10.3 vs 9.2 months, respectively; $P = .67$) or OS (13.9 vs 11.9 months; $P = .53$).

Immunotherapy

Immunotherapy has been evaluated in the maintenance setting in several trials. In a single-arm, phase 2 trial, 65 patients with AOC who responded to carboplatin plus docetaxel or paclitaxel, or to oxaliplatin plus liposomal doxorubicin and who had elevated serum levels of VEGF were treated with IL-2 and RA.[56] The median PFS was 23.2 months, and the median OS was 52.8 months. In another randomized trial, 300 patients with AOC who responded to surgery and/or chemotherapy were randomized to IFN-alFa2a or observation.[57] No benefit for interferon maintenance was seen in terms of either overall or clinical event-free survival.

Breast cancer

In patients with ER (estrogen receptor)– and/or PR (progesterone receptor)–positive metastatic breast cancer (MBC), standard therapy consists of antiestrogen or aromatase inhibitor continuation therapy. In HER2 (human epidermal growth factor receptor 2/neu–expressing metastatic breast cancer, continuation therapy with trastuzumab is the mainstay of treatment. Chemotherapy is indicated in patients with hormone receptor–negative or rapidly progressing MBC, and for visceral or endocrine-therapy–resistant disease. For these patients, maintenance therapy is not an established concept yet. Recently, several agents have been evaluated as maintenance therapy in MBC, including pegylated liposomal doxorubicin, IL-2 with RA, paclitaxel, and capecitabine. Of these, only PLD has shown improvement in TTP in a phase 3 trial trial (see infra; Table 2).

Chemotherapy

In the GEICAM 2001-01 trial, 155 patients with MBC who did not progress after doxorubicin plus docetaxel were randomized to PLD or observation.[58] PLD compared with observation significantly improved TTP by 3.3 months (8.4 vs 5.1 months, respectively; HR, 0.54; 95% CI, 0.39-0.76; $P = .0002$). However, OS was not significantly prolonged with PLD (24.8 vs 22.0 months, respectively; HR, 0.86; 95% CI, 0.58-1.27; $P = .44$). In the MANTA1 study, 255 patients with MBC who had a response to epirubicin or doxorubicin with paclitaxel were randomized to 8 courses of maintenance paclitaxel or no additional chemotherapy.[59] The study was prematurely concluded after a futility analysis found no significant difference in PFS in the paclitaxel and control arms (8.0 vs 9.0 months, respectively) or OS (28.0 vs 29.0 months). In a recent retrospective study, 64 patients who were treated with maintenance capecitabine after responding to first-line treatment were evaluated.[60] The median TTP of maintenance therapy was 4 months (range, 1-20 months). After maintenance therapy, 32.2% of the patients obtained clinical benefit, whereas 81.36% preserved the previous response.

Immunotherapy

In a phase 2 trial, 100 patients with MBC who did not progress after they received epirubicin plus paclitaxel were treated with IL-2 and RA.[61] After a median follow-up of 49 months, the median PFS and OS were 37.1 and 57.5 months, respectively. In addition, 68 patients with ER-positive tumors had a response rate similar to that of 23 patients with ER-negative tumors, but the positive patients had significantly longer PFS (44.7 vs 32.7 months, respectively) and OS (64.5 vs 51.4 months).

Carcinoma of any primary site

Immunotherapy has been evaluated in 2 single-arm, phase II trials in patients responding to first-line therapy for any cancer. Maintenance therapy was given for 1 year and consisted of administration of recombinant IL-2 plus medroxyprogesterone acetate and antioxidants. In the 28 patients enrolled in the first study, the median OS was not reached and the median PFS was 21.5 months (range, 1-40 months or more).[62] The second study enrolled 42 patients, most of whom had either head and neck cancer or lung cancer, and 88% of whom had locally advanced or metastatic disease at diagnosis. The median duration of response was 19 months, and the median PFS was 33 months.[63]

Head and neck cancer

There are few trials using maintenance therapy in metastatic head and neck cancer, and none is designed to

evaluate the maintenance phase of the trial. Clinical trials that are set up to specifically evaluate the role of maintenance therapy are needed. However, a phase 2 trial evaluated immunotherapy in the maintenance setting only. In that trial, 54 patients with recurrent metastatic squamous cell carcinoma of the head and neck who showed response to a combination of docetaxel, ifosfamide, and cisplatin were treated with maintenance IL-2 with 13-cis RA. The median PFS and OS were 11.1 and 21.8 months, respectively.[64]

Melanoma

At this time, the role of maintenance therapy in metastatic melanoma is not clear. Both ipilimumab and immunotherapy are candidates for maintenance therapy, but their role has yet to be established.

Ipilimumab

The Food and Drug Administration recently approved the use of ipilimumab, a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4, as induction therapy in metastatic melanoma based on a recent phase 3 trial.[65] In that trial, both ipilumumab alone and ipilumumab plus glycoprotein 100 showed improved survival over glycoprotein 100 alone (10 and 10.1 months, respectively, vs 6.4 months). This trial did not include a maintenance phase, but a recent phase 2 trial did.[66] Patients without progressive disease after ipilimumab induction could enter the maintenance phase beginning at week 24 until progression. Of 214 patients, 20 received maintenance therapy, but PFS and OS of this patient population were not separately reported. A single-arm trial of ipilimumab as continuation maintenance is currently ongoing.

Immunotherapy

IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used as maintenance therapy in patients with metastatic melanoma who do not progress after combined therapy with cisplatin, vinblastine, dacarbazine, IL-2, and IFN.[67] Of the 133 patients included in the trial, 79 entered the maintenance phase, of whom 4 (5%) had a better response than that achieved after induction biochemotherapy. PFS was 9 months and OS was 13.5 months, with a 12-month survival of 57% and 24-month survival of 23%. However, the results of the maintenance phase were not reported separately. In an earlier single-arm trial, patients with response to biochemotherapy were treated with IL-2 and GM-CSF maintenance therapy.[68] The median PFS was 8.1 months, compared with historical controls in whom PFS was 5.9 months ($P = .0015$); and OS was 18.5 months, compared with 9.3 months ($P = .0004$).

Other agents

Several agents (including celecoxib, arsenic trioxide, perifosine, and fotemustine have been used in the maintenance phase of trials. However, only one trial, which compared fotemustine maintenance with dacarbazine, reported the results of the maintenance phase. The best overall response rate was higher in the fotemustine arm (15.5%) than in the dacarbazine arm (7.2%; $P = .053$; odds ratio, 2.35; 95% CI, 0.97-5.71).[69]

Brain tumors

There have been very few trials that have evaluated maintenance therapy in brain tumors. In a phase 2 trial, 23 patients with high-grade glioma in CR after first-line multimodal treatment were treated with maintenance RA until progression. Median TTP was 41 weeks, and OS was 74 weeks.[70] In several other trials, various regimens (including sorafenib and cilengitide) have been used as continuation therapy or maintenance, but none was set up to establish the role of these agents in the maintenance setting.

Renal cell carcinoma

Maintenance therapy is not an established concept in metastatic renal cell carcinoma (MRCC). Immunotherapy with IL-2 and IFN-alfa have been evaluated both as continuation therapy as well as continuation maintenance therapy in clear cell MRCC. [71-74] However, none of the trials has primarily evaluated these agents in the maintenance setting. Targeted therapies—including sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, and bevacizumab (with IFN-alfa)—have all been evaluated as continuation therapy, but currently have no role as continuation maintenance or switch maintenance therapy.

Urothelial carcinoma

Maintenance intravesical therapy is standard treatment for superficial bladder cancer, but there is no such standard at this time for advanced urothelial or bladder cancers. Only gefitinib has been evaluated as continuation maintenance in a phase 2 trial.[75] Trials involving sunitinib[76] and bevacizumab (NCT00942331) in the maintenance setting are ongoing.

Both gefitinib and sunitinib have been evaluated as maintenance therapy in advanced urothelial carcinoma. In the phase 2 CALGB (Cancer and Leukemia Group B) 90102 trial, patients were treated with a combination of cisplatin, gemcitabine, and gefitinib for 6 cycles. Patients who responded to treatment or who had SD continued gefitinib as maintenance therapy until tumor progression.[75] The median duration of response for the 23 confirmed responders was 7.1 months (95% CI, 5.1–8.9). A phase 2 trial evaluating maintenance sunitinib or placebo

in patients with advanced urothelial carcinoma who have SD or better after chemotherapy is ongoing.[76] The phase 3 CALGB 90601 (NCT00942331) is currently ongoing. In this trial, patients with metastatic or unresectable urothelial carcinoma with progressive metastatic or locally advanced disease are randomized to a combination of gemcitabine, cisplatin and placebo for 6 cycles, followed by placebo until progression, or to a combination of gemcitabine, cisplatin and bevacizumab, followed by bevacizumab until progression.

Prostate cancer

Androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, or gonadotropin-releasing hormone (GnRH) agonists are used as neoadjuvant therapy in androgen-sensitive localized cancer, and as continuation therapy in androgen-sensitive recurrent or metastatic prostate cancer. For metastatic, castration-resistant prostate cancer (CRPC), therapeutic options include chemotherapy with docetaxel or cabazitaxel, immunotherapy with sipuleucel-T, or continuation therapy with abiraterone acetate. There is currently no established continuation maintenance or switch maintenance therapy in patients with prostate cancer. However, several phase 2 trials are currently exploring the role of maintenance therapy in these patients, as discussed infra.

Temsirolimus and sunitinib

In an ongoing trial, patients with CRPC who responded to 6 to 9 cycles of docetaxel-based chemotherapy (defined as >50% decline in PSA from baseline, or response according to RECIST [Response Evaluation Criteria in Solid Tumors]), receive weekly maintenance temsirolimus until progression.[77] Of the 10 patients who have been enrolled, 6 patients have discontinued because of treatment failure. Mean time to failure was 5.3 cycles (range, 3-8 cycles). Maintenance sunitinib in patients with metastatic CRPC who have either SD or a response to docetaxel is currently being evaluated in a multicenter phase II trial.[78] So far, no PFS data have been presented.

Immunotherapy

In an ongoing trial, patients with CRPC who completed 10 to 12 cycles of docetaxel or mitoxantrone without progression and who had a median PSA of 56.5 (range, 0.1-566) received maintenance GM-CSF until disease progression.[79] Preliminary results after a median follow-up of 11 months (range, 2-17 months), show that 3 patients have SD and 2 have PR for an overall clinical benefit of 50%. One patient remains on the study at 7 months; the median response duration for the other 4 responding patients was 7 months. BPX-101, a drug-activated autologous dendritic cell vaccine that targets prostate specific membrane antigen, is currently being evaluated as induction therapy (every 2 weeks for 6 doses) followed by maintenance therapy (every 8 weeks in a dose escalation trial in patients with metastatic CRPC who have SD, PR, or CR after docetaxel.[80] No results specific to the maintenance phase of the trial have been published yet.

TABLE 3 Phase 2 trials with regimens that had encouraging results

Disease	Agent	Type of maintenance therapy
NSCLC	L-BLP25[21]	Switch
	IL-2/RA[20]	Switch
Malignant pleural mesothelioma	Pemetrexed[30]	Continuation
	IL-2[31]	Switch
Colorectal cancer	Capecitabine[35]	Switch
	UFT[38]	Switch
	IL-2/RA[40]	Switch
Pancreatic and biliary tree carcinoma	IL-2/RA[41]	Switch
Ovarian	Pegylated liposomal doxorubicin[47]	Switch
	Pegylated liposomal doxorubicin[48]	Continuation
	Carboplatin[49]	Continuation
	BIBF 1120[54]	Switch
	IL-2/RA[56]	Switch
Breast cancer	IL-2/RA[61]	Switch
Carcinoma of any primary site	IL-2/medroxyprogesterone acetate/antioxidants[62,63]	Switch
Head and neck cancer	IL-2/RA[64]	Switch
Melanoma	IL-2/GM-CSF[68]	Continuation
High-grade glioma	RA[70]	Switch
Urothelial cancer	Gefitinib[75]	Continuation

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin-2; L-BLP25, BLP25 liposome vaccine; NSCLC, non–small cell lung cancer; RA, retinoic acid; UFT, uracil-tegafur.

Discussion

To date, there have been promising results for maintenance therapy in metastatic NSCLC and colorectal cancer. Although an increasing number of phase 2 trials are evaluating this treatment strategy in other solid tumors, there have been very few randomized, controlled trials. To be able to truly evaluate the role of maintenance therapy,

we need randomized clinical trials that are specifically designed to evaluate maintenance therapy. Furthermore, not only should overall survival and progression-free survival be included in the study as end points, but also quality of life and toxicity (both immediate and cumulative). Progression-free survival is currently used as a primary end point in most studies, with overall survival as secondary end point. It is important to be aware that the effect of maintenance therapy on overall survival may be hard to elucidate, as further lines of treatment upon disease progression can potentially confound overall survival.

Although maintenance therapy is being increasingly investigated in the setting of metastatic solid tumors, it is becoming an established concept only in a few. Maintenance therapy may not work in one type of metastatic solid tumor and may work well in another. With agreement in terminology and with trials designed to specifically evaluate the effect of maintenance therapy, future trials will be able to better address the role of maintenance therapy in metastatic solid tumors. Table 3.

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